UNITED STATES PATENT
APPLICATION OF

ALICIA REGUEIRO-REN
69 Greenview Terrace
Middletown, CT 06457

QIUFEN MAY XUE
75 Barrington Way
Glastonbury, CT 06033

JOHN F. KADOW
9 Quarry Run
Wallingford, CT 06492

MALCOLM TAYLOR
57 Evenlode Drive
Didcot, Oxfordshire
OX11 7XQ United Kingdom

FOR

INDOLE, AZAINDOLE AND RELATED HETEROCYCLIC UREIDO AND THIOUREIDO PIPERAZINE DERIVATIVES

EXPRESS MIALING LABEL NO. EV 272264489US

DATE OF DEPOSIT July 18, 2003

I HEREBY CERTIFY THAT THE ATTACHED CORRESPONDENCE AND DOCUMENTS ARE BEING DEPOSITED WITH THE U.S. POSTAL SERVICE "EXPRESS MAIL POST OFFICE TO ADDRESSEE" SERVICE UNDER 37 CFR 1.10 ON THE DATE INDICATED ABOVE AND IS ADDRESSED TO THE COMMISSIONER FOR PATENTS, P.O. BOX 1450, ALEXANDRIA, VA 22313-1450.

Annamarie Bodisch 7/18/2003
(Signature) (Date)

INDOLE, AZAINDOLE AND RELATED HETEROCYCLIC UREIDO AND THIOUREIDO PIPERAZINE DERIVATIVES

REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application Serial Number 60/398,812 filed July 25, 2002.

FIELD OF THE INVENTION

This invention provides compounds having drug and bio-affecting properties, their pharmaceutical compositions and method of use. In particular, the invention is concerned with new heterocyclic ureido and thioureido piperazines derivatives that possess unique antiviral activity. More particularly, the present invention relates to compounds useful for the treatment of HIV and AIDS.

BACKGROUND ART

HIV-1 (human immunodeficiency virus -1) infection remains a major medical problem, with an estimated 42 million people infected worldwide at the end of 2002. The number of cases of HIV and AIDS (acquired immunodeficiency syndrome) has risen rapidly. In 2002, ~5.0 million new infections were reported, and 3.1 million people died from AIDS. Currently available drugs for the treatment of HIV include nine nucleoside reverse transcriptase (RT) inhibitors or approved single pill combinations(zidovudine or AZT (or Retrovir®), didanosine (or Videx®), stavudine (or Zerit®), lamivudine (or 3TC or Epivir®), zalcitabine (or DDC or Hivid®), abacavir succinate (or Ziagen®), Tenofovir disoproxil fumarate salt (or Viread®), Combivir® (contains -3TC plus AZT), Trizivir® (contains abacavir, lamivudine, and zidovudine); three non-nucleoside reverse transcriptase inhibitors: nevirapine (or Viramune®), delavirdine (or Rescriptor®)

and efavirenz (or Sustiva®), and eight peptidomimetic protease inhibitors or approved formulations: saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, Kaletra®(lopinavir and Ritonavir), and Atazanavir (Reyataz®). Each of these drugs can only transiently restrain viral replication if used alone. However, when used in combination, these drugs have a profound effect on viremia and disease progression. In fact, significant reductions in death rates among AIDS patients have been recently documented as a consequence of the widespread application of combination therapy. However, despite these impressive results, 30 to 50% of patients ultimately fail combination drug therapies. Insufficient drug potency, non-compliance, restricted tissue penetration and drug-specific limitations within certain cell types (e.g. most nucleoside analogs cannot be phosphorylated in resting cells) may account for the incomplete suppression of sensitive viruses. Furthermore, the high replication rate and rapid turnover of HIV-1 combined with the frequent incorporation of mutations, leads to the appearance of drug-resistant variants and treatment failures when sub-optimal drug concentrations are present (Larder and Kemp; Gulick; Kuritzkes; Morris-Jones *et al*; Schinazi *et al*; Vacca and Condra; Flexner; Berkhout and Ren *et al*; (Ref. 6-14)). Therefore, novel anti-HIV agents exhibiting distinct resistance patterns, and favorable pharmacokinetic as well as safety profiles are needed to provide more treatment options.

Currently marketed HIV-1 drugs are dominated by either nucleoside reverse transcriptase inhibitors or peptidomimetic protease inhibitors. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have recently gained an increasingly important role in the therapy of HIV infections (Pedersen & Pedersen, Ref 15). At least 30 different classes of NNRTI have been described in the literature (De Clercq, Ref. 16) and several NNRTIs have been evaluated in clinical trials. Dipyridodiazepinone (nevirapine), benzoxazinone (efavirenz) and bis(heteroaryl) piperazine derivatives (delavirdine) have been approved for clinical use. However, the major drawback to the development and application of NNRTIs is the propensity for rapid emergence of drug resistant strains, both in tissue cell culture and in treated individuals, particularly those subject to

monotherapy. As a consequence, there is considerable interest in the identification of NNRTIs less prone to the development of resistance (Pedersen & Pedersen, Ref 15). A recent overview of non-nucleoside reverse transcriptase inhibitors: perspectives on novel therapeutic compounds and strategies for the treatment of HIV infection. has appeared (Buckheit , reference 99). A review covering both NRTI and NNRTIs has appeared (De clercq, reference 100). An overview of the current state of the HIV drugs has been published (De clercq, reference 101).

Several indole derivatives including indole-3-sulfones, piperazino indoles, pyrazino indoles, and 5H-indolo[3,2-b][1,5]benzothiazepine derivatives have been reported as HIV-1 reverse transciptase inhibitors (Greenlee et al, Ref. 1; Williams et al, Ref. 2; Romero et al, Ref. 3; Font et al, Ref. 17; Romero et al, Ref. 18; Young et al, Ref. 19; Genin et al, Ref. 20; Silvestri et al, Ref. 21). Indole 2-carboxamides have also been described as inhibitors of cell adhesion and HIV infection (Boschelli et al, US 5,424,329, Ref. 4). 3-substituted indole natural products (Semicochliodinol A and B, didemethylasterriquinone and isocochliodinol) were disclosed as inhibitors of HIV-1 protease (Fredenhagen et al, Ref. 22).

Structurally related aza-indole amide derivatives have been disclosed previously (Kato et al, Ref. 23; Levacher et al, Ref. 24; Dompe Spa, WO-09504742, Ref. 5(a); SmithKline Beecham PLC, WO-09611929, Ref. 5(b); Schering Corp., US-05023265, Ref. 5(c)). However, these structures differ from those claimed herein in that they are aza-indole mono-amide rather than unsymmetrical aza-indole piperazine ureido and thioureido derivatives, and there is no mention of the use of these compounds for treating viral infections, particularly HIV. Indole and azaindole piperazine containing derivatives have been disclosed in four different PCT and issued U.S. patent applications (Reference 93-95, 106). PCT International Patent Application WO9951224 by Bernd Nickel et.al. (reference 107) describes N-indolylglyoxamides for the treatment of cancer. The substitution patterns on the piperazine are outside the

scope of the indoles covered by this invention. A patent application describing a method for treating cystic fibrosis (Reference 108) describes the use of indole containing compounds which are generally somewhat similar to those in reference 107 and this art is included for completeness.

None of these applications discloses ureido and thioureido piperazines compounds such as described in this invention for the treatment of antiviral diseases and HIV.

Nothing in these references can be construed to disclose or suggest the novel compounds of this invention and their use to inhibit HIV infection.

REFERENCES CITED

Patent documents

1. Greenlee, W.J.; Srinivasan, P.C. Indole reverse transcriptase inhibitors. U.S. Patent 5,124,327.

2. Williams, T.M.; Ciccarone, T.M.; Saari, W. S.; Wai, J.S.; Greenlee, W.J.; Balani, S.K.; Goldman, M.E.; Theohrides, A.D. Indoles as inhibitors of HIV reverse transcriptase. European Patent 530907.

3. Romero, D.L.; Thomas, R.C.; Preparation of substituted indoles as anti-AIDS pharmaceuticals. PCT WO 93 / 01181.

4. Boschelli, D.H.; Connor, D.T.; Unangst, P.C. Indole-2-carboxamides as inhibitors of cell adhesion. U.S. Patent 5,424,329.

5. (a) Mantovanini, M.; Melillo, G.; Daffonchio, L. Tropyl 7-azaindol-3-ylcarboxyamides as antitussive agents. PCT WO 95/04742 (Dompe Spa). (b) Cassidy, F.; Hughes, I.; Rahman, S.; Hunter, D. J. Bisheteroaryl-carbonyl and

carboxamide derivatives with 5HT 2C/2B antagonists activity. PCT WO 96/11929. (c) Scherlock, M. H.; Tom, W. C. Substituted 1*H*-pyrrolopyridine-3-carboxamides. U. S. Patent 5,023,265.

Other Publications

6. Larder, B.A.; Kemp, S.D. Multiple mutations in the HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*, **1989**, *246*,1155-1158.

7. Gulick, R.M. Current antiretroviral therapy: An overview. *Quality of Life Research*, **1997**, *6*, 471-474.

8. Kuritzkes, D.R. HIV resistance to current therapies. *Antiviral Therapy*, **1997**, *2* (Supplement 3), 61-67.

9. Morris-Jones, S.; Moyle, G.; Easterbrook, P.J. Antiretroviral therapies in HIV-1 infection. *Expert Opinion on Investigational Drugs*, **1997**, *6*(8),1049-1061.

10. Schinazi, R.F.; Larder, B.A.; Mellors, J.W. Mutations in retroviral genes associated with drug resistance. *International Antiviral News*, **1997**, *5*,129-142,.

11. Vacca, J.P.; Condra, J.H. Clinically effective HIV-1 protease inhibitors. *Drug Discovery Today*, **1997**, *2*, 261-272.

12. Flexner, D. HIV-protease inhibitors. *Drug Therapy*, **1998**, *338*, 1281-1292.

13. Berkhout, B. HIV-1 evolution under pressure of protease inhibitors: Climbing the stairs of viral fitness. *J. Biomed. Sci.*, **1999**, *6*, 298-305.

14. Ren, S.; Lien, E. J. Development of HIV protease inhibitors: A survey. *Prog. Drug Res.*, **1998**, *51*, 1-31.

15. Pedersen, O.S.; Pedersen, E.B. Non-nucleoside reverse transcriptase inhibitors: the NNRTI boom. *Antiviral Chem. Chemother.* **1999**, *10*, 285-314.

16. (a) De Clercq, E. The role of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV-1 infection. *Antiviral Research*, **1998**, *38*, 153-179. (b) De Clercq, E. Perspectives of non-nucleoside reverse transcriptase inhibitors (NNRTIs) in the therapy of HIV infection. IL. *Farmaco*, **1999**, *54*, 26-45.

17. Font, M.; Monge, A.; Cuartero, A.; Elorriaga, A.; Martinez-Irujo, J.J.; Alberdi, E.; Santiago, E.; Prieto, I.; Lasarte, J.J.; Sarobe, P. and Borras, F. Indoles and pyrazino[4,5-*b*]indoles as nonnucleoside analog inhibitors of HIV-1 reverse transcriptase. *Eur. J. Med. Chem.*, **1995**, *30*, 963-971.

18. Romero, D.L.; Morge, R.A.; Genin, M.J.; Biles, C.; Busso, M,; Resnick, L.; Althaus, I.W.; Reusser, F.; Thomas, R.C and Tarpley, W.G. Bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure-activity relationships of novel substituted indole analogues and the identification of 1-[(5-methanesulfonamido-1H-indol-2-yl)-carbonyl]-4-[3-[1-methylethyl)amino]-pyridinyl]piperazine momomethansulfonate (U-90152S), a second generation clinical candidate. *J. Med. Chem.*, **1993**, *36*, 1505-1508.

19. Young, S.D.; Amblard, M.C.; Britcher, S.F.; Grey, V.E.; Tran, L.O.; Lumma, W.C.; Huff, J.R.; Schleif, W.A.; Emini, E.E.; O'Brien, J.A.; Pettibone, D.J. 2-Heterocyclic indole-3-sulfones as inhibitors of HIV-reverse transcriptase. *Bioorg. Med. Chem. Lett.*, **1995**, *5*, 491-496.

20. Genin, M.J.; Poel, T.J.; Yagi, Y.; Biles, C.; Althaus, I.; Keiser, B.J.; Kopta, L.A.; Friis, J.M.; Reusser, F.; Adams, W.J.; Olmsted, R.A.; Voorman,

R.L.; Thomas, R.C. and Romero, D.L. Synthesis and bioactivity of novel bis(heteroaryl)piperazine (BHAP) reverse transcriptase inhibitors: structure-activity relationships and increased metabolic stability of novel substituted pyridine analogs. *J. Med. Chem.*, **1996**, *39*, 5267-5275.

21. Silvestri, R.; Artico, M.; Bruno, B.; Massa, S.; Novellino, E.; Greco, G.; Marongiu, M.E.; Pani, A.; De Montis, A and La Colla, P. Synthesis and biological evaluation of 5*H*-indolo[3,2-*b*][1,5]benzothiazepine derivatives, designed as conformationally constrained analogues of the human immunodeficiency virus type 1 reverse transcriptase inhibitor L-737,126. *Antiviral Chem. Chemother.* **1998**, *9*, 139-148.

22. Fredenhagen, A.; Petersen, F.; Tintelnot-Blomley, M.; Rosel, J.; Mett, H and Hug, P. J. Semicochliodinol A and B: Inhibitors of HIV-1 protease and EGF-R protein Tyrosine Kinase related to Asterriquinones produced by the fungus *Chrysosporium nerdarium*. *Antibiotics*, **1997**, *50*, 395-401.

23. Kato, M.; Ito, K.; Nishino, S.; Yamakuni, H.; Takasugi, H. New 5-HT_3 (Serotonin-3) receptor antagonists. IV. Synthesis and structure-activity relationships of azabicycloalkaneacetamide derivatives. *Chem. Pharm. Bull.*, **1995**, *43*, 1351-1357.

24. Levacher, V.; Benoit, R.; Duflos, J; Dupas, G.; Bourguignon, J.; Queguiner, G. Broadening the scope of NADH models by using chiral and non chiral pyrrolo [2,3-*b*] pyridine derivatives. *Tetrahedron*, **1991**, *47*, 429-440.

25. Shadrina, L.P.; Dormidontov, Yu.P.; Ponomarev, V,G.; Lapkin, I.I. Reactions of organomagnesium derivatives of 7-aza- and benzoindoles with diethyl oxalate and the reactivity of ethoxalylindoles. *Khim. Geterotsikl. Soedin.*, **1987**, 1206-1209.

26. Sycheva, T.V.; Rubtsov, N.M.; Sheinker, Yu.N.; Yakhontov, L.N. Some reactions of 5-cyano-6-chloro-7-azaindoles and lactam-lactim tautomerism in 5-cyano-6-hydroxy-7-azaindolines. *Khim. Geterotsikl. Soedin.*, **1987**, 100-106.

27. (a) Desai, M.; Watthey, J.W.H.; Zuckerman, M. A convenient preparation of 1-aroylpiperazines. *Org. Prep. Proced. Int.*, **1976**, *8*, 85-86. (b) Adamczyk, M.; Fino, J.R. Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and desethylprocainamide. *Org. Prep. Proced. Int.* **1996**, *28*, 470-474. (c) Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (*S*)-piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.*, **1995**, *36*, 6419-6422. (d) Wang, T.; Zhang, Z.; Meanwell, N.A. Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. *J. Org. Chem.*, **1999**, *64*, 7661-7662.

28. Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT): A new coupling reagent with remarkable resistance to racemization. *Organic Lett.*, **1999**, *1*, 91-93.

29. Harada, N.; Kawaguchi, T.; Inoue, I.; Ohashi, M.; Oda, K.; Hashiyama, T.; Tsujihara, K. Synthesis and antitumor activity of quaternary salts of 2-(2'-oxoalkoxy)-9-hydroxyellipticines. *Chem. Pharm. Bull.*, **1997**, *45*, 134-137.

30. Schneller, S. W.; Luo, J.-K. Synthesis of 4-amino-1*H*-pyrrolo[2,3-*b*]pyridine (1,7-Dideazaadenine) and 1*H*-pyrrolo[2,3-*b*]pyridin-4-ol (1,7-Dideazahypoxanthine). *J. Org. Chem.*, **1980**, *45*, 4045-4048.

31. Shiotani, S.; Tanigochi, K. Furopyridines. XXII [1]. Elaboration of the *C*-substitutents *alpha* to the heteronitrogen atom of furo[2,3-*b*]-, -[3.2-*b*]-, -[2.3-*c*]- and -[3,2-*c*]pyridine. *J. Het. Chem.*, **1997**, *34*, 901-907.

32. Minakata, S.; Komatsu, M.; Ohshiro, Y. Regioselective functionalization of 1*H*-pyrrolo[2,3-*b*]pyridine via its N-oxide. *Synthesis*, **1992**, 661-663.

33. Klemm, L. H.; Hartling, R. Chemistry of thienopyridines. XXIV. Two transformations of thieno[2,3-*b*]pyridine 7-oxide (1). *J. Het. Chem.*, **1976**, *13*, 1197-1200.

34. Antonini, I.; Claudi, F.; Cristalli, G.; Franchetti, P.; Crifantini, M.; Martelli, S. Synthesis of 4-amino-1-□-D-ribofuranosyl-1*H*-pyrrolo[2,3-*b*]pyridine (1-Deazatubercidin) as a potential antitumor agent. *J. Med. Chem.*, **1982**, *25*, 1258-1261.

35. (a) Regnouf De Vains, J.B.; Papet, A.L.; Marsura, A. New symmetric and unsymmetric polyfunctionalized 2,2'-bipyridines. *J. Het. Chem.*, **1994**, *31*, 1069-1077. (b) Miura, Y.; Yoshida, M.; Hamana, M. Synthesis of 2,3-fused quinolines from 3-substituted quinoline 1-oxides. Part II, *Heterocycles*, **1993**, *36*, 1005-1016. (c) Profft, V.E.; Rolle, W. Uber 4-merkaptoverbindungendes 2-methylpyridins. *J. Prakt. Chem.*, **1960**, *283* (11), 22-34.

36. Nesi, R.; Giomi, D.; Turchi, S.; Tedeschi, P., Ponticelli, F. A new one step synthetic approach to the isoxazolo[4,5-*b*]pyridine system. *Synth. Comm.*, **1992**, *22*, 2349-2355.

37. (a) Walser, A.; Zenchoff, G.; Fryer, R.I. Quinazolines and 1,4-benzodiazepines. 75. 7-Hydroxyaminobenzodiazepines and derivatives. *J. Med. Chem.*, **1976**, *19*, 1378-1381. (b) Barker, G.; Ellis, G.P. Benzopyrone. Part I. 6-Amino- and 6-hydroxy-2-subtituted chromones. *J. Chem. Soc.*, **1970**, 2230-2233.

38. Ayyangar, N.R.; Lahoti, R J.; Daniel, T. An alternate synthesis of 3,4-diaminobenzophenone and mebendazole. *Org. Prep. Proced. Int.*, **1991**, *23*, 627-631.

39. Mahadevan, I.; Rasmussen, M. Ambident heterocyclic reactivity: The alkylation of pyrrolopyridines (azaindoles, diazaindenes). *Tetrahedron*, **1993**, *49*, 7337-7352.

40. Chen, B.K.; Saksela, K.; Andino, R.; Baltimore, D. Distinct modes of human immunodeficiency type 1 proviral latency revealed by superinfection of nonproductively infected cell lines with recombinant luciferase-encoding viruses. *J. Virol.*, **1994**, *68*, 654-660.

41. Bodanszky, M.; Bodanszky, A. *"The Practice of Peptide Synthesis"* 2nd Ed., Springer-Verlag: Berlin Heidelberg, Germany, **1994**.

42. Albericio, F. *et al. J. Org. Chem.* **1998**, *63*, 9678.

43. Knorr, R. *et al. Tetrahedron Lett.* **1989**, *30*, 1927.

44. (a) Jaszay Z. M. *et al. Synth. Commun.*, **1998** *28*, 2761 and references cited therein; (b) Bernasconi, S. *et al. Synthesis*, **1980**, 385.

45. (a) Jaszay Z. M. *et al. Synthesis*, **1989**, 745 and references cited therein; (b) Nicolaou, K. C. *et al. Angew. Chem. Int. Ed.* **1999**, *38*, 1669.

46. Ooi, T. *et al. Synlett.* **1999**, 729.

47. Ford, R. E. *et al. J. Med. Chem.* **1986**, *29*, 538.

48. (a) Yeung, K.-S. *et al.* Bristol-Myers Squibb Unpublished Results. (b) Wang, W. *et al. Tetrahedron Lett.* **1999**, *40*, 2501.

49. Brook, M. A. *et al. Synthesis*, **1983**, 201.

50. Yamazaki, N. *et al. Tetrahedron Lett.* **1972**, 5047.

51. Barry A. Bunin "The Combinatorial Index" 1998 Academic Press, San Diego / London pages 78-82.

52. Richard C. Larock Comprehensive Organic Transormations 2nd Ed. 1999, John Wiley and Sons New York.

53. M.D. Mullican et.al. *J.Med. Chem.* **1991**, *34*, 2186-2194.

54. Protective groups in organic synthesis 3rd ed. / Theodora W. Greene and Peter G.M. Wuts. New York : Wiley, 1999.

55. Katritzky, Alan R. Lagowski, Jeanne M. The principles of heterocyclic ChemistryNew York : Academic Press, 1968

56. Paquette, Leo A. Principles of modern heterocyclic chemistry New York : Benjamin.

57. Katritzky, Alan R.; Rees, Charles W.; Comprehensive heterocyclic chemistry : the structure, reactions, synthesis, and uses of heterocyclic compounds 1st ed.Oxford (Oxfordshire) ; New York : Pergamon Press, 1984. 8 v.

58. Katritzky, Alan RHandbook of heterocyclic 1st edOxford (Oxfordshire) ; New York : Pergamon Press, 1985.

59. Davies, David I Aromatic Heterocyclic Oxford ; New York : Oxford University Press, 1991.

60. Ellis, G. P. Synthesis of fused Chichester [Sussex] ; New York : Wiley, c1987-c1992. Chemistry of heterocyclic compounds ; v. 47.

61. Joule, J. A Mills, K. ,Smith, G. F. Heterocyclic Chemistry , 3rd ed London ;New York Chapman & Hall, 1995.

62. Katritzky, Alan R., Rees, Charles W. , Scriven, Eric F. V. Comprehensive heterocyclic chemistry II : a review of the literature 1982-1995.

63. The structure, reactions, synthesis, and uses of heterocyclic compounds 1st ed. Oxford ; New York : Pergamon, 1996. 11 v. in 12 : ill. ; 28 cm.

64. Eicher, Theophil, Hauptmann, Siegfried. The chemistry of heterocycles : structure, reactions, syntheses, and applications Stuttgart ; New York : G. Thieme, 1995.

65. Grimmett, M. R. Imidazole and benzimidazole Synthesis London ; San Diego : Academic Press, 1997.

66. Advances in heterocyclic chemistry. Published in New York by Academic Press, starting in 1963-present.

67. Gilchrist, T. L. (Thomas Lonsdale) Heterocyclic chemistry 3rd ed. Harlow, Essex : Longman, **1997**. 414 p. : ill. ; 24 cm.

68. Farina, Vittorio; Roth, Gregory P. Recent advances in the Stille reaction; *Adv. Met.-Org. Chem.* **1996**, *5*, 1-53.

69. Farina, Vittorio; Krishnamurthy, Venkat; Scott, William J. The Stille reaction ; Org. React. (N. Y.) (1997), *50*, 1-652.

70. Stille, J. K. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508-524.

71. Norio Miyaura and Akiro Suzuki *Chem Rev.* **1995**, *95*, 2457.

72. Home, D.A. *Heterocycles* **1994**, *39*, 139.

73. Kamitori, Y. et.al. *Heterocycles*, **1994**, *37(1)*, 153.

74. Shawali, J. *Heterocyclic Chem.* **1976**, *13*, 989.

75. a) Kende, A.S.et al. *Org. Photochem. Synth.* **1972**, *1*, 92. b) Hankes, L.V.; *Biochem. Prep.* **1966**, *11*, 63. c) *Synth. Meth. 22*, 837.

76. Hulton et. al. *Synth. Comm.* **1979**, *9*, 789.

77. Pattanayak, B.K. et.al. *Indian J. Chem.* **1978**, *16*, 1030.

78. *Chemische Berichte* **1902**, *35*, 1545.

79. *Chemische Berichte* Ibid **1911**, *44*, 493.

80. Moubarak, I., Vessiere, R. *Synthesis* **1980**, Vol. 1, 52-53.

81. *Ind J. Chem.* **1973**, *11*, 1260.

82. Roomi et.al. *Can J. Chem.* **1970**, *48*, 1689.

83. Sorrel, T.N. *J. Org. Chem.* **1994**, *59*, 1589.

84. Nitz, T.J. et. al. *J. Org. Chem.* **1994**, *59*, 5828-5832.

85. Bowden, K. et.al. *J. Chem. Soc.* **1946**, 953.

86. Nitz, T.J. et. al. *J. Org. Chem.* **1994**, *59*, 5828-5832.

87. Scholkopf et. al. *Angew. Int. Ed. Engl.* **1971**, *10(5)*, 333.

88. (a) Behun, J. D.; Levine, R. *J. Org. Chem.* **1961**, *26*, 3379. (b) Rossen, K.; Weissman, S.A.; Sager, J.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. Asymmetric Hydrogenation of tetrahydropyrazines: Synthesis of (*S*)-

piperazine 2-tert-butylcarboxamide, an intermediate in the preparation of the HIV protease inhibitor Indinavir. *Tetrahedron Lett.*, **1995**, *36*, 6419-6422. (c) Jenneskens, L. W.; Mahy, J.; den Berg, E. M. M. de B.-v.; Van der Hoef, I.; Lugtenburg, J. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 97.

89. Wang, T.; Zhang, Z.; Meanwell, N.A. Benzoylation of Dianions: Preparation of mono-Benzoylated Symmetric Secondary Diamines. *J. Org. Chem.*, **1999**, *64*, 7661-7662.

90. (a) Adamczyk, M.; Fino, J.R. Synthesis of procainamide metabolites. N-acetyl desethylprocainamide and desethylprocainamide. *Org. Prep. Proced. Int.* **1996**, *28*, 470-474. (b) Wang, T.; Zhang, Z.; Meanwell, N.A. Regioselective mono-Benzoylation of Unsymmetrical Piperazines. *J. Org. Chem.*, in press.

91. Masuzawa, K.; Kitagawa, M.; Uchida, H. *Bull Chem. Soc. Jpn.* **1967**, *40*, 244-245.

92. Furber, M.; Cooper, M. E.; Donald, D. K. *Tetrahedron Lett.* **1993**, *34*, 1351-1354.

93. Blair, Wade S.; Deshpande, Milind; Fang, Haiquan; Lin, Pin-fang; Spicer, Timothy P.; Wallace, Owen B.; Wang, Hui; Wang, Tao; Zhang, Zhongxing; Yeung, Kap-sun. Preparation of antiviral indoleoxoacetyl piperazine derivatives US patent 6,469,006. Preparation of antiviral indoleoxoacetyl piperazine derivatives. PCT Int. Appl. (PCT/US00/14359), WO 0076521 A1, filed May 24, 2000, published December 21, 2000.

94. Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.; Bender, John A. Antiviral azaindole derivatives. U.S. patent 6476034 and Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.; Bender, John A. Preparation of antiviral azaindole derivatives. PCT Int. Appl.

(PCT/US01/02009), WO 0162255 A1, filed January 19, 2001, published August 30, 2001.

95. Wallace, Owen B.; Wang, Tao; Yeung, Kap-Sun; Pearce, Bradley C.; Meanwell, Nicholas A.; Qiu, Zhilei; Fang, Haiquan; Xue, Qiufen May; Yin, Zhiwei. Composition and antiviral activity of substituted indoleoxoacetic piperazine derivatives. U.S. Patent Application Serial Number 10/027,612 filed December 19, 2001, which is a continuation-in-part application of U.S. Serial Number 09/888,686 filed June 25, 2001 (corresponding to PCT Int. Appl. (PCT/US01/20300), WO 0204440 A1, filed June 26, 2001, published January 17, 2002.

96. J. L. Marco, S. T. Ingate, and P. M. Chinchon Tetrahedron 1999, 55, 7625-7644.

97. C. Thomas, F. Orecher, and P.Gmeiner Synthesis 1998, 1491.

98. M. P. Pavia, S. J. Lobbestael, C. P. Taylor, F. M. Hershenson, and D. W. Miskell.

99. Buckheit, Robert W., Jr. Expert Opinion on Investigational Drugs 2001, 10(8), 1423-1442.

100. Balzarini, J.; De Clercq, E.. Antiretroviral Therapy 2001, 31-62.

101. E. De clercq Journal of Clinical Virology, 2001, 22, 73-89.

102. Merour, Jean-Yves; Joseph, Benoit. Curr. Org. Chem. (2001), 5(5), 471-506.

103. T. W. von Geldern et al. J. Med. Chem 1996, 39, 968.

104. M. Abdaoui et al. Tetrahedron 2000, 56, 2427.

105. W. J. Spillane et al. J. Chem. Soc., Perkin Trans. 1, 1982, 3, 677

106. Wang, Tao; Wallace, Owen B.; Zhang, Zhongxing; Meanwell, Nicholas A.; Kadow, John F. Yin, Zhiwei. Composition and Antiviral Activity of Substituted Azaindoleoxoacetic Piperazine Derivatives. U.S. Patent Application Serial Number 10/214,982 filed August 7, 2002, which is a continuation-in-part application of U.S. Serial Number 10/038,306 filed January 2, 2002 (corresponding to PCT Int. Appl. (PCT/US02/00455), WO 02/062423 A1, filed January 2, 2002, published August 15, 2002.

107. Preparation of indolylglyoxylamides as antitumor agents, Nickel, Bernd; Szelenyi, Istvan; Schmidt, Jurgen; Emig, Peter; Reichert, Dietmar; Gunther, Eckhard; Brune, Kay PCT Int. Appl. WO 9951224.

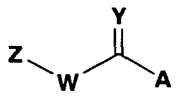
108. Method to Treat Cystic fibrosis Higgins, Linda S.; Liu, David Y.; Protter, Andrew, A. PCT Int. Appl. WO 03/041644.

SUMMARY OF THE INVENTION

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to a virus such as HIV. The compounds of Formula I, which include nontoxic pharmaceutically acceptable salts and/or hydrates thereof, have the formula and meaning as described below. Each embodiment of a particular aspect of the invention depends from the preceding embodiment unless otherwise stated.

The present invention comprises compounds of Formula I, or pharmaceutically acceptable salts thereof, which are effective antiviral agents, particularly as inhibitors of HIV.

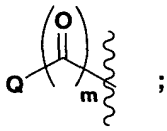
A first embodiment of the invention are compounds of Formula I, including pharmaceutically acceptable salts thereof,



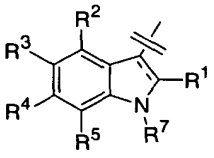
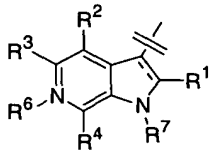
(I)

wherein:

Y is O or S;

Z is  ;

Q is selected from the group consisting of

 and  ;

R^1 is hydrogen;

R^2 is hydrogen, methoxy or halogen;

R^3, R^4, and R^5, are independently selected from the group consisting of hydrogen, halogen, cyano, nitro, $COOR^8$, XR^9, and B;

m is 2;

R^6 is O or does not exist;

R^7 is hydrogen or methyl;

- - represents a carbon-carbon bond;

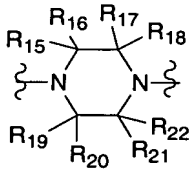
A is $NR^{13}R^{14}$;

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl; wherein said (C_{1-6})alkyl and phenyl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F; or R^{13} and R^{14} taken together with the nitrogen atom to which they are attached forms a heteroalicyclic ring containing 4 to 6 atoms;

heteroaryl is selected from the group consisting of pyridinyl, pyrazinyl, pyridazinyl, pyrimidinyl, furanyl, thienyl, benzothienyl, thiazolyl, isothiazolyl, oxazolyl, benzooxazolyl, isoxazolyl, imidazolyl, benzoimidazolyl, 1H-imidazo[4,5-b]pyridin-2-yl, 1H-imidazo[4,5-c]pyridin-2-yl, oxadiazolyl, thiadiazolyl, pyrazolyl, tetrazolyl, tetrazinyl, triazinyl, triazolyl, quinolinyl, and isoquinolyl;

heteroalicyclic ring is selected from the group consisting of azetidinyl, piperidyl, piperazinyl, morpholinyl, pyrrolidinyl, thiomorpholinyl and tetrahydropyranyl;

-W- is



;

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} are each independently H or (C_{1-6})alkyl; wherein (C_{1-6})alkyl is optionally substituted with one to three same or different

members selected from the group consisting of halogen; with the proviso that a maximum of two of R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} are not hydrogen;

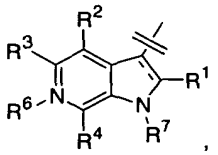
B is selected from the group consisting of (C_{1-6})alkyl, (C_{3-6})cycloalkyl, $C(O)NR^{23}R^{24}$, phenyl and heteroaryl; wherein said (C_{1-6})alkyl, phenyl and heteroaryl are independently optionally substituted with one to three same or different halogens or from one to three same or different substituents selected from F;

F is selected from the group consisting of (C_{1-6})alkyl, phenyl, hydroxy, (C_{1-6})alkoxy, halogen, benzyl, $-NR^{25}C(O)-(C_{1-6})$alkyl, $-NR^{26}R^{27}$, $COOR^{28}$ and $-CONR^{29}R^{30}$; wherein said (C_{1-6})alkyl is optionally substituted with one to three same or different halogen;

R^8, R^9 and R^{28} are selected from the group consisting of hydrogen and (C_{1-6})alkyl;

X is selected from the group consisting of NR^{31}, O and S; and

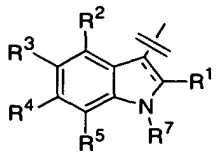
R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{29}, R^{30}, R^{31} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl, (C_{1-6})alkoxy, phenyl and heteroaryl; wherein said phenyl and heteroaryl are independently optionally substituted with one to three same or different halogen, methyl, or CF_3 groups; with the proviso that when Q is



then

R^2 and R^4, cannot both be hydrogen; and

with the further proviso that when Q is


, then

R^2 and R^5, cannot both be hydrogen.

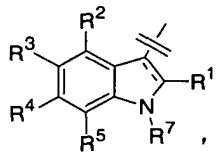
A preferred embodiment of the invention are compounds wherein:

R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21}, R^{22} are each independently H or methyl; wherein only one or zero of R^{15}, R^{16}, R^{17}, R^{18}, R^{19}, R^{20}, R^{21} and R^{22} is methyl;

Y is O; and

Q is a member selected from groups (A) and (B) consisting of

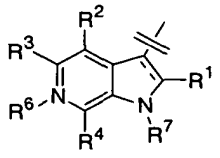
(A)


,

provided R^3 and R^4 are each hydrogen; and

R^5 is selected from the group consisting of halogen, cyano, methoxy, $COOR^8$, $C(O)NHCH_3$, C(O)NHheteroaryl, and heteroaryl; and

(B)


,

provided R^3 is hydrogen;

R^4 is selected from the group consisting of hydrogen, halogen, methoxy, cyano, $COOR^8$, $C(O)NHCH_3$, C(O)NHheteroaryl and heteroaryl; and R^6 does not exist.

Another preferred embodiment are compounds wherein:

R^{13} and R^{14} are independently selected from the group consisting of hydrogen, (C_{1-6})alkyl and phenyl; or taken together with the nitrogen atom to which they are attached forms a pyrrolidinyl or morpholinyl ring.

Another embodiment of the present invention is a method for treating mammals infected with a virus, wherein said virus is HIV, comprising administering to said mammal an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, excipients or diluents; optionally the compound of Formula I, including said salts thereof, can be administered in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

Another embodiment of the present invention is a pharmaceutical composition comprising an antiviral effective amount of a compound of Formula I, including pharmaceutically acceptable salts thereof, and one or more pharmaceutically acceptable carriers, excipients, diluents and optionally in combination with an antiviral effective amount of an AIDS treatment agent selected from the group consisting of: (a) an AIDS antiviral agent; (b) an anti-infective agent; (c) an immunomodulator; and (d) HIV entry inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

Since the compounds of the present invention, may possess asymmetric centers and therefore occur as mixtures of diastereomers and enantiomers, the

present invention includes the individual diastereoisomeric and enantiomeric forms of the compounds of Formula I in addition to the mixtures thereof.

DEFINITIONS

The term "C_{1-6} alkyl" as used herein and in the claims (unless specified otherwise) mean straight or branched chain alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, amyl, hexyl and the like.

"Halogen" refers to chlorine, bromine, iodine or fluorine.

An "aryl" group refers to an all carbon monocyclic or fused-ring polycyclic (i.e., rings which share adjacent pairs of carbon atoms) groups having a completely conjugated pi-electron system. Examples, without limitation, of aryl groups are phenyl, napthalenyl and anthracenyl. The aryl group may be substituted or unsubstituted. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino and -NR^xR^y, wherein R^x and R^y are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, carbonyl, C-carboxy, sulfonyl, trihalomethyl, and, combined, a five- or six-member heteroalicyclic ring.

As used herein, a "heteroaryl" group refers to a monocyclic or fused ring (i.e., rings which share an adjacent pair of atoms) group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur and, in addition, having a completely conjugated pi-electron system. Unless otherwise indicated, the heteroaryl group may be attached at either a carbon or nitrogen atom within the heteroaryl group. It should be noted that the term heteroaryl is intended to encompass an N-oxide of the parent heteroaryl if such an

N-oxide is chemically feasible as is known in the art. Examples, without limitation, of heteroaryl groups are furyl, thienyl, benzothienyl, thiazolyl, imidazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, benzothiazolyl, triazolyl, tetrazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyranyl, tetrahydropyranyl, pyrazolyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, purinyl, carbazolyl, benzoxazolyl, benzimidazolyl, indolyl, isoindolyl, pyrazinyl. diazinyl, pyrazine, triazinyltriazine, tetrazinyl, and tetrazolyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, O-carbamyl, N-carbamyl, C-amido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethyl, ureido, amino, and $-NR^xR^y$, wherein R^x and R^y are as defined above.

As used herein, a "heteroalicyclic" group refers to a monocyclic or fused ring group having in the ring(s) one or more atoms selected from the group consisting of nitrogen, oxygen and sulfur. Rings are selected from those which provide stable arrangements of bonds and are not intended to encomplish systems which would not exist. The rings may also have one or more double bonds. However, the rings do not have a completely conjugated pi-electron system. Examples, without limitation, of heteroalicyclic groups are azetidinyl, piperidyl, piperazinyl, imidazolinyl, thiazolidinyl, 3-pyrrolidin-1-yl, morpholinyl, thiomorpholinyl and tetrahydropyranyl. When substituted the substituted group(s) is preferably one or more selected from alkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halogen, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$, wherein R^x and R^y are as defined above.

An "alkyl" group refers to a saturated aliphatic hydrocarbon including straight chain and branched chain groups. Preferably, the alkyl group has 1 to 20 carbon atoms (whenever a numerical range; e.g., "1-20", is stated herein, it means that the group, in this case the alkyl group may contain 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc. up to and including 20 carbon atoms). More preferably, it is a medium size alkyl having 1 to 10 carbon atoms. Most preferably, it is a lower alkyl having 1 to 4 carbon atoms. The alkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from trihaloalkyl, cycloalkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalomethanesulfonamido, trihalomethanesulfonyl, and combined, a five- or six-member heteroalicyclic ring.

A "cycloalkyl" group refers to an all-carbon monocyclic or fused ring (i.e., rings which share and adjacent pair of carbon atoms) group wherein one or more rings does not have a completely conjugated pi-electron system. Examples, without limitation, of cycloalkyl groups are cyclopropane, cyclobutane, cyclopentane, cyclopentene, cyclohexane, cyclohexadiene, cycloheptane, cycloheptatriene and adamantane. A cycloalkyl group may be substituted or unsubstituted. When substituted, the substituent group(s) is preferably one or more individually selected from alkyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, heteroaryloxy, heteroalicycloxy, thiohydroxy, thioalkoxy, thioaryloxy, thioheteroaryloxy, thioheteroalicycloxy, cyano, halo, nitro, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, C-thioamido, N-amido, C-carboxy, O-carboxy, sulfinyl, sulfonyl, sulfonamido, trihalo- methanesulfonamido, trihalomethanesulfonyl, silyl, guanyl, guanidino, ureido, phosphonyl, amino and $-NR^xR^y$ with R^x and R^y as defined above.

An "alkenyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon double bond.

An "alkynyl" group refers to an alkyl group, as defined herein, consisting of at least two carbon atoms and at least one carbon-carbon triple bond.

A "hydroxy" group refers to an –OH group.

An "alkoxy" group refers to both an –O-alkyl and an –O-cycloalkyl group as defined herein.

An "aryloxy" group refers to both an –O-aryl and an –O-heteroaryl group, as defined herein.

A "heteroaryloxy" group refers to a heteroaryl-O- group with heteroaryl as defined herein.

A "heteroalicycloxy" group refers to a heteroalicyclic-O- group with heteroalicyclic as defined herein.

A "thiohydroxy" group refers to an –SH group.

A "thioalkoxy" group refers to both an S-alkyl and an –S-cycloalkyl group, as defined herein.

A "thioaryloxy" group refers to both an –S-aryl and an –S-heteroaryl group, as defined herein.

A "thioheteroaryloxy" group refers to a heteroaryl-S- group with heteroaryl as defined herein.

A "thioheteroalicycloxy" group refers to a heteroalicyclic-S- group with heteroalicyclic as defined herein.

A "carbonyl" group refers to a –C(=O)-R" group, where R" is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), as each is defined herein.

An "aldehyde" group refers to a carbonyl group where R" is hydrogen.

A "thiocarbonyl" group refers to a –C(=S)-R" group, with R" as defined herein.

A "Keto" group refers to a –CC(=O)C- group wherein the carbon on either or both sides of the C=O may be alkyl, cycloalkyl, aryl or a carbon of a heteroaryl or heteroaliacyclic group.

A "trihalomethanecarbonyl" group refers to a $Z_3CC(=O)$- group with said Z being a halogen.

A "C-carboxy" group refers to a –C(=O)O-R" groups, with R" as defined herein.

An "O-carboxy" group refers to a R"C(-O)O-group, with R" as defined herein.

A "carboxylic acid" group refers to a C-carboxy group in which R" is hydrogen.

A "trihalomethyl" group refers to a $-CZ_3$, group wherein Z is a halogen group as defined herein.

A "trihalomethanesulfonyl" group refers to an $Z_3CS(=O)_2$- groups with Z as defined above.

A "trihalomethanesulfonamido" group refers to a $Z_3CS(=O)_2NR^X$- group with Z and R^X as defined herein.

A "sulfinyl" group refers to a –S(=O)-R" group, with R" as defined herein and, in addition, as a bond only; i.e., -S(O)-.

A "sulfonyl" group refers to a $–S(=O)_2R$" group with R" as defined herein and, in addition as a bond only; i.e., $-S(O)_2-$.

A "S-sulfonamido" group refers to a $–S(=O)_2NR^XR^Y$, with R^X and R^Y as defined herein.

A "N-Sulfonamido" group refers to a $R"S(=O)_2NR_X$- group with R_x as defined herein.

A "O-carbamyl" group refers to a $–OC(=O)NR^xR^y$ as defined herein.

A "N-carbamyl" group refers to a $R^xOC(=O)NR^y$ group, with R^x and R^y as defined herein.

A "O-thiocarbamyl" group refers to a $–OC(=S)NR^xR^y$ group with R^x and R^y as defined herein.

A "N-thiocarbamyl" group refers to a $R^xOC(=S)NR^y$- group with R^x and R^y as defined herein.

An "amino" group refers to an $–NH_2$ group.

A "C-amido" group refers to a $-C(=O)NR^xR^y$ group with R^x and R^y as defined herein.

A "C-thioamido" group refers to a $-C(=S)NR^xR^y$ group, with R^x and R^y as defined herein.

A "N-amido" group refers to a $R^xC(=O)NR^y-$ group, with R^x and R^y as defined herein.

An "ureido" group refers to a $-NR^xC(=O)NR^yR^{y2}$ group with R^x and R^y as defined herein and R^{y2} defined the same as R^x and R^y.

An "thioureido" group refers to a $-NR^xC(=S)NR^yR^{y2}$ group with R^x and R^y as defined herein and R^{y2} defined the same as R^x and R^y.

A "guanidino" group refers to a $-R^xNC(=N)NR^yR^{y2}$ group, with R^x, R^y and R^{y2} as defined herein.

A "guanyl" group refers to a $R^xR^yNC(=N)-$ group, with R^x and R^Y as defined herein.

A "cyano" group refers to a $-CN$ group.

A "silyl" group refers to a $-Si(R'')_3$, with R" as defined herein.

A "phosphonyl" group refers to a $P(=O)(OR^x)_2$ with R^x as defined herein.

A "hydrazino" group refers to a $-NR^xNR^yR^{y2}$ group with R^x, R^y and R^{y2} as defined herein.

Any two adjacent R groups may combine to form an additional aryl, cycloalkyl, heteroaryl or heterocyclic ring fused to the ring initially bearing those R groups.

It is known in the art that nitogen atoms in heteroaryl systems can be "participating in a heteroaryl ring double bond", and this refers to the form of double bonds in the two tautomeric structures which comprise five-member ring heteroaryl groups. This dictates whether nitrogens can be substituted as well understood by chemists in the art. The disclosure and claims of the present invention are based on the known general principles of chemical bonding. It is understood that the claims do not encompass structures known to be unstable or not able to exist based on the literature.

Physiologically acceptable salts and prodrugs of compounds disclosed herein are within the scope of this invention. The term "pharmaceutically acceptable salt" as used herein and in the claims is intended to include nontoxic base addition salts. Suitable salts include those derived from organic and inorganic acids such as, without limitation, hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, tartaric acid, lactic acid, sulfinic acid, citric acid, maleic acid, fumaric acid, sorbic acid, aconitic acid, salicylic acid, phthalic acid, and the like. The term "pharmaceutically acceptable salt" as used herein is also intended to include salts of acidic groups, such as a carboxylate, with such counterions as ammonium, alkali metal salts, particularly sodium or potassium, alkaline earth metal salts, particularly calcium or magnesium, and salts with suitable organic bases such as lower alkylamines (methylamine, ethylamine, cyclohexylamine, and the like) or with substituted lower alkylamines (e.g. hydroxyl-substituted alkylamines such as diethanolamine, triethanolamine or tris(hydroxymethyl)- aminomethane), or with bases such as piperidine or morpholine.

In the method of the present invention, the term "antiviral effective amount" means the total amount of each active component of the method that is

sufficient to show a meaningful patient benefit, i.e., healing of acute conditions characterized by inhibition of the HIV infection. When applied to an individual active ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously. The terms "treat, treating, treatment" as used herein and in the claims means preventing or ameliorating diseases associated with HIV infection.

The present invention is also directed to combinations of the compounds with one or more agents useful in the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table.

ANTIVIRALS

Drug Name	Manufacturer	Indication
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse trans-criptase (RT) inhibitor)
Amprenivir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)

Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir
Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which Neutralizes pH Labile alpha aberrant Interferon	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
AR177	Aronex Pharm	HIV infection, AIDS, ARC
Beta-fluoro-ddA	Nat'l Cancer Institute	AIDS-associated diseases
BMS-232623 (CGP-73547)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)

BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012	Warner-Lambert	HIV-1 infection
Cidofovir	Gilead Science	CMV retinitis, herpes, papillomavirus
Curdlan sulfate	AJI Pharma USA	HIV infection
Cytomegalovirus Immune globin	MedImmune	CMV retinitis
Cytovene	Syntex	Sight threatening
Ganciclovir		CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic
ddC Dideoxycytidine	Hoffman-La Roche	HIV infection, AIDS, ARC
ddI Dideoxyinosine	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)

Efavirenz (DMP 266) (-)6-Chloro-4-(S)-cyclopropylethynyl-4(S)-trifluoro-methyl-1,4-dihydro-2H-3,1-benzoxazin-2-one, STOCRINE	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)
Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Almeda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS

Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boeheringer Ingleheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc.	CMV retinitis, HIV infection, other CMV infections
PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)

Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston, TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann-LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy-thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	Genital HSV & CMV infections
Virazole Ribavirin	Viratek/ICN (Costa Mesa, CA)	asymptomatic HIV positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-LaRoche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies
Tenofovir disoproxil, fumarate salt (Viread®)	Gilead	HIV infection, AIDS, (reverse transcriptase inhibitor)

Combivir®	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
abacavir succinate (or Ziagen®)	GSK	HIV infection, AIDS, (reverse transcriptase inhibitor)
REYATAZ® (or atazanavir)	Bristol-Myers Squibb	HIV infection AIDs, protease inhibitor
FUZEON (or T-20)	Roche / Trimeris	HIV infection AIDs, viral Fusion inhibitor

IMMUNOMODULATORS

Drug Name	Manufacturer	Indication
AS-101	Wyeth-Ayerst	AIDS
Bropirimine	Pharmacia Upjohn	Advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	Blocks HIV fusion with CD4+ cells

Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoechst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	Seropositive HIV
IL-2 Interleukin-2	Cetus	AIDS, in combination w/AZT
IL-2 Interleukin-2	Hoffman-LaRoche Immunex	AIDS, ARC, HIV, in combination w/AZT
IL-2 Interleukin-2 (aldeslukin)	Chiron	AIDS, increase in CD4 cell counts
Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	Pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC

Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine-Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE Muramyl-Tripeptide	Ciba-Geigy Corp.	Kaposi's sarcoma
Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	Immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection
Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

Drug Name	Manufacturer	Indication
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	Cryptococcal meningitis, candidiasis
Pastille Nystatin Pastille	Squibb Corp.	Prevention of oral candidiasis
Ornidyl Eflornithine	Merrell Dow	PCP
Pentamidine Isethionate (IM & IV)	LyphoMed (Rosemont, IL)	PCP treatment
Trimethoprim		Antibacterial
Trimethoprim/sulfa		Antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine Isethionate for Inhalation	Fisons Corporation	PCP prophylaxis
Spiramycin	Rhone-Poulenc	Cryptosporidial diarrhea
Intraconazole-R51211	Janssen-Pharm.	Histoplasmosis; cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	Severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	Treatment of anorexia assoc. W/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	Diarrhea and malabsorption related to AIDS

Additionally, the compounds of the invention herein may be used in combination with another class of agents for treating AIDS which are called HIV entry inhibitors. Examples of such HIV entry inhibitors are discussed in DRUGS OF THE FUTURE 1999, 24(12), pp. 1355-1362; CELL, Vol. 9, pp. 243-246, Oct. 29, 1999; and DRUG DISCOVERY TODAY, Vol. 5, No. 5, May 2000, pp. 183-194.

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives, HIV entry inhibitors or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse

transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is the sulfate salt of N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

Abbreviations

The following abbreviations, most of which are conventional abbreviations well known to those skilled in the art, are used throughout the description of the invention and the examples. Some of the abbreviations used are as follows:

h	=	hour(s)
rt	=	room temperature
mol	=	mole(s)

	mmol	=	millimole(s)
	g	=	gram(s)
	mg	=	milligram(s)
	mL	=	milliliter(s)
	TEA	=	triethylamine
	TFA	=	Trifluoroacetic Acid
	DCE	=	1,2-Dichloroethane
	CH_2Cl_2	=	Dichloromethane
	TPAP	=	tetrapropylammonium perruthenate
	THF	=	Tetrahydofuran
	DEPBT	=	3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
	DMAP	=	4-dimethylaminopyridine
	P-EDC	=	Polymer supported 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	EDC	=	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	DMF	=	*N,N*-dimethylformamide
	Hunig's Base	=	*N,N*-Diisopropylethylamine
	mCPBA	=	*meta*-Chloroperbenzoic Acid
	azaindole	=	1*H*-Pyrrolo-pyridine
	4-azaindole	=	1*H*-pyrrolo[3,2-*b*]pyridine
	5-azaindole	=	1*H*-Pyrrolo[3,2-*c*]pyridine
	6-azaindole	=	1*H*-pyrrolo[2,3-*c*]pyridine
	7-azaindole	=	1*H*-Pyrrolo[2,3-*b*]pyridine
	PMB	=	4-Methoxybenzyl
	DDQ	=	2, 3-Dichloro-5, 6-dicyano-1, 4-benzoquinone
	OTf	=	Trifluoromethanesulfonoxy
	NMM	=	4-Methylmorpholine
	PIP-COPh	=	1-Benzoylpiperazine
	NaHMDS	=	Sodium hexamethyldisilazide
	EDAC	=	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
	TMS	=	Trimethylsilyl

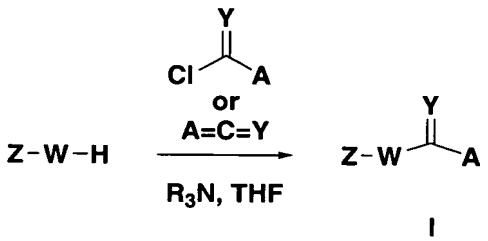
DCM	=	Dichloromethane
DCE	=	Dichloroethane
MeOH	=	Methanol
THF	=	Tetrahydrofuran
EtOAc	=	Ethyl Acetate
LDA	=	Lithium diisopropylamide
TMP-Li	=	2,2,6,6-tetramethylpiperidinyl lithium
DME	=	Dimethoxyethane
DIBALH	=	Diisobutylaluminum hydride
HOBT	=	1-hydroxybenzotriazole
CBZ	=	Benzyloxycarbonyl
PCC	=	Pyridinium chlorochromate

Chemistry

The present invention comprises compounds of Formula I, their pharmaceutical formulations, and their use in patients suffering from or susceptible to HIV infection. The compounds of Formula I include pharmaceutically acceptable salts thereof.

The synthesis procedures and anti-HIV-1 activities of indoleoxoacetic ureido and thioureido piperazine containing analogs are below.

Scheme A



I

Compounds of formula I can be obtained from compounds of formula Z-W-H in the presence of a tertiary amine (3-10 eq.) such as triethylamine or diisopropylethylamine in an anhydrous aprotic solvent such as THF, acetonitrile or DMF at temperatures ranging from 0°C using either a carbamoyl chloride or an isocyanate (2-3 eq) to obtain compounds of formula I where Y is O; or using thiocarbamoyl chloride or an isothiocyanate (2-3 eq.) to obtain compounds of formula I where Y is S. The reaction can be monitored by LC/MS.

The starting materials carbamoyl chlorides, isocyanates, thiocarbamoyl chlorides and isothiocyanates can be purchased from commercial sources (e.g. Aldrich Chemical Co.). When making compound I where A is $-NR^{13}R^{14}$, the carbamoyl or thiocarbamoyl chloride,  (where Y is O or S, and A is $-NR^{13}R^{14}$) is used. When making compounds I where A is $-NHR^{13}$, the isocyanate or thioisocyanate, A=C=Y (where Y is O or S, and A is $-NR^{13}$) is used.

It should be noted that in many cases reactions are depicted for only one position of an intermediate, such as the R^5 position, for example. It is to be understood that such reactions could be used at other positions, such as R^2-R^4, of the various intermediates. Reaction conditions and methods given in the specific examples are broadly applicable to compounds with other substitution and other tranformations in this application. The following schemes describe general reaction schemes for taking appropriately substituted Q (indoles and azaindoles) and converting them to compounds of Formula I. While these schemes are very general, other permutations such as carrying a precursor or precursors to substituents R^2 through R^5 through the reaction scheme and then converting it to a compound of Formula I in the last step are also contemplated methods of this invention. Nonlimiting examples of such strategies follow in subsequent schemes.

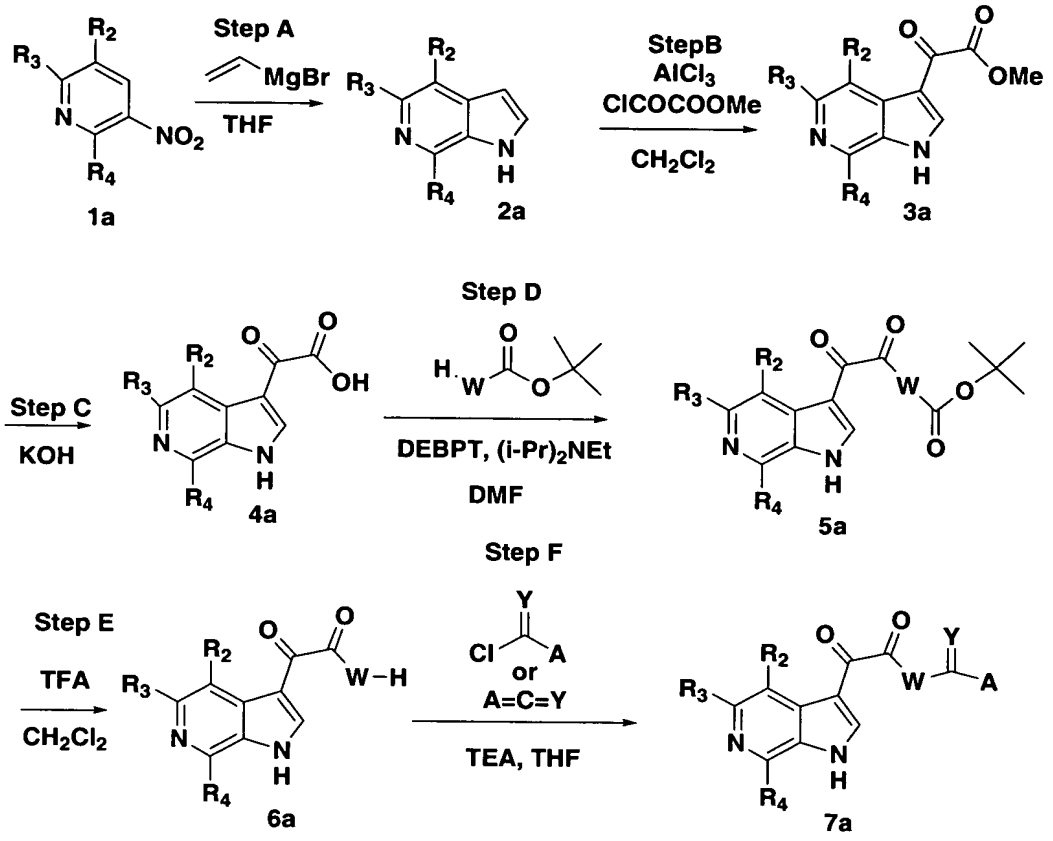
In addition to procedures for preparing Q and Z, procedures for coupling piperazine amides to oxoacetyl derivatives are described in the Blair, Wang,

Wallace, or Wang references 93-95 and 106 respectively. The entire disclosures in U.S Patent 6,469,006 granted October 22, 2002; U.S. Patent 6,476,034 granted November 5, 2002; U.S. Patent Application Serial Number 10/027,612 filed December 19, 2001, which is a continuation-in-part of U.S. Serial Number 09/888,686 filed June 25, 2001 (corresponding to PCT WO 02/04440, published January 17, 2002); and U.S. Patent Application Serial Number 10/214,982 filed August 7, 2002, which is a continuation-in-part of U.S. Serial Number 10/038,306 filed January 2, 2002 (corresponding to PCT WO 02/62423 published August 15, 2002) are incorporated by reference herein. The procedures used to couple indole or azaindole oxoacetic acids to piperazine amides in these references can be used analogously to form the compounds of this invention except the piperazine carbamates or thiocarbamates are used in place of the piperazine benzamides. It should be stated that the procedures incorporated from these applications encompass the preparation of starting materials and transformations which are useful for enabling the preparation of compounds of this invention.

Procedures for making Z (as defined in formula I of the description of the invention) are described in the Blair, Wang, Wallace, or Wang references 93-95 and 106 respectively. The entire disclosures in U.S Patent 6,469,006 granted October 22, 2002; U.S. Patent 6,476,034 granted November 5, 2002; U.S. Patent Application Serial Number 10/027,612 filed December 19, 2001, which is a continuation-in-part of U.S. Serial Number 09/888,686 filed June 25, 2001 (corresponding to PCT WO 02/04440, published January 17, 2002); and U.S. Patent Application Serial Number 10/214,982 filed August 7, 2002, which is a continuation-in-part of U.S. Serial Number 10/038,306 filed January 2, 2002 (corresponding to PCT WO 02/62423 published August 15, 2002) are incorporated by reference herein.

Additional general procedures to construct substituted azaindole Q and Z of Formula I and intermediates useful for their synthesis are described in the following Schemes.

Scheme 1



Step A in Scheme 1 depicts the synthesis of an aza indole intermediate, 2a via the well known Bartoli reaction in which vinyl magnesium bromide reacts with an aryl or heteroaryl nitro group, such as in 1, to form a five-membered nitrogen containing ring as shown. Some references for the above transformation include: Bartoli et al. a) *Tetrahedron Lett.* **1989**, *30*, 2129. b) *J. Chem. Soc. Perkin Trans. 1* **1991**, 2757. c) *J. Chem. Soc. Perkin Trans. II* **1991**, 657. d) Synthesis (1999), 1594. In the preferred procedure, a solution of vinyl Magnesium bromide in THF (typically 1.0M but from 0.25 to 3.0M) is added dropwise to a solution of the nitro pyridine in THF at -78° under an inert atmosphere of either nitrogen or Argon. After addition is completed, the reaction temperature is allowed to warm to -20° and then is stirred for approximately 12h before quenching with 20% aq ammonium chloride solution. The reaction is extracted with ethyl acetate and then worked up in a typical manner using a

drying agent such as anhydrous magnesium sulfate or sodium sulfate. Products are generally purified using chromatography over Silica gel. Best results are generally achieved using freshly prepared vinyl Magnesium bromide. In some cases, vinyl Magnesium chloride may be substituted for vinyl Magnesium bromide.

Substituted azaindoles may be prepared by methods described in the literature or may be available from commercial sources. Thus there are many methods for carrying out step A in the literature and the specific examples are too numerous to even list. A review on the synthesis of 7-azaindoles has been published (Merour et. al. reference 102). Alternative syntheses of aza indoles and general methods for carrying out step A include, but are not limited to, those described in the following references (a-k below): a) Prokopov, A. A.; Yakhontov, L. N. *Khim.-Farm. Zh.* **1994**, *28(7)*, 30-51; b) Lablache-Combier, A. **Heteroaromatics.** Photoinduced Electron Transfer **1988**, Pt. C, 134-312; c) Saify, Zafar Said. *Pak. J. Pharmacol.* **1986**, *2(2)*, 43-6; d) Bisagni, E. *Jerusalem Symp. Quantum Chem. Biochem.* **1972**, *4*, 439-45; e) Yakhontov, L. N. *Usp. Khim.* **1968**, *37(7)*, 1258-87; f) Willette, R. E. *Advan. Heterocycl. Chem.* **1968**, *9*, 27-105; g) Mahadevan, I.; Rasmussen, M. *Tetrahedron* **1993**, *49(33)*, 7337-52; h) Mahadevan, I.; Rasmussen, M. *J. Heterocycl. Chem.* **1992**, *29(2)*, 359-67; i) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64(26)*, 9430-9443; j) Spivey, A.C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39(48)*, 8919-8922; k) Advances in Heterocyclic Chemistry (Academic press) **1991**, *Vol. 52*, pg 235-236 and references therein.

Step B. Intermediate 3a can be prepared by reaction of aza-indole, intermediate 2a, with an excess of ClCOCOOMe in the presence of $AlCl_3$ (aluminum chloride) (Sycheva et al, Ref. 26, Sycheva, T.V.; Rubtsov, N.M.; Sheinker, Yu.N.; Yakhontov, L.N. Some reactions of 5-cyano-6-chloro-7-azaindoles and lactam-lactim tautomerism in 5-cyano-6-hydroxy-7-azaindolines. *Khim. Geterotsikl. Soedin.*, **1987**, 100-106). Typically an inert solvent such as CH_2Cl_2 is used but others such as THF, Et_2O, DCE, dioxane, benzene, or toluene

may find applicability either alone or in mixtures. Other oxalate esters such as ethyl or benzyl mono esters of oxalic acid could also suffice for either method shown above. More lipophilic esters ease isolation during aqueous extractions. Phenolic or substituted phenolic (such as pentafluorophenol) esters enable direct coupling of the HW-protecting group, such as a Boc-piperazine, in Step D without activation. Lewis acid catalysts, such as tin tetrachloride, titanium IV chloride, and aluminum chloride are employed in Step B with aluminum chloride being most preferred. Alternatively, the azaindole is treated with a Grignard reagent such as MeMgI (methyl magnesium iodide), methyl magnesium bromide or ethyl magnesium bromide and a zinc halide, such as $ZnCl_2$ (zinc chloride) or zinc bromide, followed by the addition of an oxalyl chloride mono ester, such as ClCOCOOMe (methyl chlorooxoacetate) or another ester as above, to afford the aza-indole glyoxyl ester (Shadrina et al, Ref. 25). Oxalic acid esters such as methyl oxalate, ethyl oxalate or as above are used. Aprotic solvents such as CH_2Cl_2, Et_2O, benzene, toluene, DCE, tert butyl methyl ether or the like may be used alone or in combination for this sequence. In addition to the oxalyl chloride mono esters, oxalyl chloride itself may be reacted with the azaindole and then further reacted with an appropriate amine, such as a piperazine derivative.

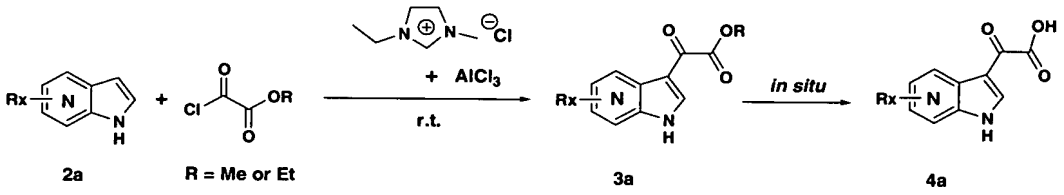
Step C. Hydrolysis of the methyl ester, (intermediate 3a, Scheme 1) affords a potassium salt of intermediate 4a, which is coupled with protected piperazine derivatives, such as BOC-piperazine, as shown in Step D of Scheme 1. Some typical conditions employ methanolic or ethanolic sodium hydroxide followed by careful acidification with aqueous hydrochloric acid of varying molarity but 1M HCl is preferred. The acidification is not utilized in many cases as described above for the preferred conditions. Lithium hydroxide or potassium hydroxide could also be employed and varying amounts of water could be added to the alcohols. Propanols or butanols could also be used as solvents. Elevated temperatures up to the boiling points of the solvents may be utilized if ambient temperatures do not suffice. Alternatively, the hydrolysis may be carried out in a non polar solvent such as CH_2Cl_2 or THF in the presence of Triton B. Temperatures of –78 °C to the boiling point of the solvent may be employed but -

10 °C is preferred. Other conditions for ester hydrolysis are listed in reference 41 and both this reference and many of the conditions for ester hydrolysis are well known to chemists of average skill in the art.

Alternative procedures for step B and C:
Imidazolium Chloroaluminate:

We found that ionic liquid 1-alkyl-3-alkylimidazolium chloroaluminate is generally useful in promoting the Friedel-Crafts type acylation of indoles and azaindoles. The ionic liquid is generated by mixing 1-alkyl-3-alkylimidazolium chloride with aluminium chloride at room temperature with vigorous stirring. 1:2 or 1:3 molar ratio of 1-alkyl-3-alkylimidazolium chloride to aluminium chloride is preferred. One particular useful imidazolium chloroaluminate for the acylation of azaindole with methyl or ethyl chlorooxoacetate is the 1-ethyl-3-methylimidazolium chloroaluminate. The reaction is typically performed at ambient temperature and the azaindoleglyoxyl ester can be isolated. More conveniently, we found that the glyoxyl ester can be hydrolyzed *in situ* at ambient temperature on prolonged reaction time (typically overnight) to give the corresponding glyoxyl acid (intermediate 4a) for amide formation (**Scheme 2**).

Scheme 2



A representative experimental procedure is as follows: 1-ethyl-3-methylimidazolium chloride (2 equiv.; purchased from TCI; weighted under a stream of nitrogen) was stirred in an oven-dried round bottom flask at r.t. under a nitrogen atmosphere, and added aluminium chloride (6 equiv.; anhydrous powder packaged under argon in ampules purchased from Aldrich preferred; weighted

under a stream of nitrogen). The mixture was vigorously stirred to form a liquid, which was then added azaindole (1 equiv.) and stirred until a homogenous mixture resulted. The reaction mixture was added dropwise ethyl or methyl chlorooxoacetate (2 equiv.) and then stirred at r.t. for 16 h. After which time, the mixture was cooled in an ice-water bath and the reaction quenched by carefully adding excess water. The precipitates were filtered, washed with water and dried under high vacuum to give the azaindoleglyoxylic acid. For some examples, 3 equivalents of 1-ethyl-3-methylimidazolium chloride and chlorooxoacetate may be required.

Related references: (1) Welton, T. *Chem Rev.* **1999**, *99*, 2071; (2) Surette, J. K. D.; Green, L.; Singer, R. D. *Chem. Commun.* **1996**, 2753; (3) Saleh, R. Y. WO 0015594.

Step D. The acid intermediate 4a, from step C of Scheme 1 is coupled with a protected piperazine, for example t-butyl 1-piperazinecarboxylate (Boc-piperazine), preferably in the presence of DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, to provide azaindole piperazine amide (intermediate 5a). DEPBT was either purchased from Adrich or prepared according to the procedure of Ref. 28, Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Organic Lett.*, **1999**, *1*, 91-93. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used. The acid intermediate 4a from Scheme 1 (which can also be depicted as Z-OH or intermediates QC(O)C(O)OH) are coupled with either a substituted piperazine, H-W-C(=Y)-A or a protected piperazine, for example t-butyl 1-piperazinecarboxylate (Boc-piperazine, H-W-tBoc), as shown in Scheme 1 (where W corresponds to claim 1 and H is hydrogen). They can be coupled with the acid using standard amide bond or peptide bond forming coupling reagents. The combination of EDAC and triethylamine in tetrahydrofuran or BOPCl and diisopropyl ethyl amine in chloroform can be utilized most but DEPBT as mentioned above, or other coupling reagents such as PyBop could be utilized.

Another useful coupling condition employs HATU (L.A. Carpino et. al. J.Chem.Soc. Chem Comm. 1994, 201-203; A. Virgilio et.al. J.Am. Chem. Soc. 1994, 116,11580-11581). A general procedure for using this reagent is Acid (1eq) and H-W-Boc or HCl salt (2eq) in DMF are stirred at rt for between 1 h and 2 days. HATU (2eq) was added in one portion and then DMAP(3eq). The reaction was stirred at rt for 2 to 15h (reaction progress monitored by standard methods ie TLC, LC/MS). The mixture is filtered through filter paper to collect the solid. The filtrate is concentrated and water is added. The mixture is filtered again and the solid is washed with water. The solid is conbined and washed with water. Many reagents for amide bond couplings are known by an organic chemist skilled in the art and nearly all of these are applicable for realizing coupled amide products.

As mentioned above, DEPBT (3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one) and *N,N*-diisopropylethylamine, commonly known as Hunig's base, represents another efficient method to form the amide bond (step D) and provide compounds of Claim I. DEPBT is either purchased from Adrich or prepared according to the procedure of Ref. 28, Li, H.; Jiang, X.; Ye, Y.-H.; Fan, C.; Romoff, T.; Goodman, M. *Organic Lett.*, **1999**, *1*, 91-93. Typically an inert solvent such as DMF or THF is used but other aprotic solvents could be used.

Alternatively, the acid could be converted to a methyl ester using excess diazomethane in THF/ether. The methyl ester in dry THF could be reacted with the lithium amide of intermediate H-W. The lithium amide of H-W, Li-W is formed by reacting intermediate 1 with lithium bistrimethylsilylamide in THF for 30 minutes in an ice water cooling bath. Sodium or potassium amides could be formed similarly and utilized if additional reactivity is desired. Other esters such as ethyl, phenyl, or pentafluorophenyl could be utilized and would be formed using standard methodology.

The amide bond construction reaction could be carried out using the preferred conditions described above, the EDC conditions described below, other coupling conditions described in this application, or alternatively by applying the conditions or coupling reagents for amide bond construction described later in this application for construction of substituents R_2-R_5. Some specific nonlimiting examples are given in this application. In addition, the acid can be converted to the acid chloride using oxalyl chloride in a solvent such as benzene or thionyl chloride either neat or containing a catalystic amount of DMF. Temperatures between 0°C and reflux may be utilized depending on the substrate. Compounds of formula I can be obtained from the resultant compounds of formula Z-Cl by reaction with the appropriate H-W-C(=Y)-A in the presence of a tertiary amine (3-10 eq.) such as triethylamine or diisopropylethylamine in an anhydrous aprotic solvent such as dichloromethane, dichloroethane, diethyl ether, dioxane,THF, acetonitrile, DMF or the like at temperatures ranging from 0°C to reflux. Most preferred are dichloromethane, dichloroethane, or THF. The reaction can be monitored by LC/MS.

It should be noted that in many cases reactions are depicted for only one position of an intermediate, such as the R^5 position, for example. It is to be understood that such reactions could be used at other positions, such as R^2-R^4, of the various intermediates. Reaction conditions and methods given in the specific examples are broadly applicable to compounds with other substitution and other tranformations in this application. Schemes 1 and 2 describe general reaction schemes for taking appropriately substituted Q (indoles and azaindoles) and converting them to compounds of Formula I. While these schemes are very general, other permutations such as carrying a precursor or precursors to substituents R^2 through R^5 through the reaction scheme and then converting it to a compound of Formula I in the last step are also contemplated methods of this invention. Nonlimiting examples of such strategies follow in subsequent schemes.

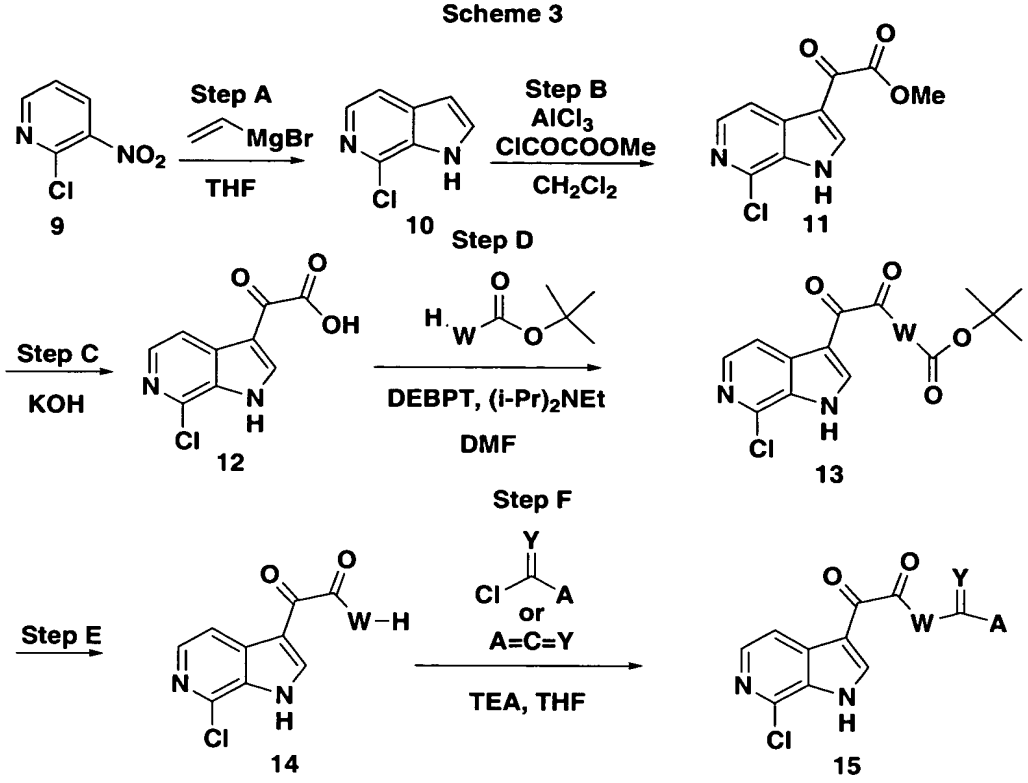
Step E. Cleaveage of the protecting group, (intermediate 5a, scheme 1) affords piperazine 6a. Some typical conditions for the removal of BOC employ acid such as HCl or TFA in a 1:1 mixture of H_2O and other solvent such as THF, MeOH or acetonitrile. Altenatively, the cleaveage can be carried out with an ahydrous solution of 20% TFA in methylene chloride.

Step F. Carbamoylation of piperazine intermediate 6a was carried out as described in scheme A. Therefore a solution of intermediate 6a in anhydrous tetrahydrofuran was treated with a carbamoyl chloride (2-3 eq.) in the presence of triethylamine (3-10eq) at room temperature for 18h to afford urea 7a.

The amide bond construction reactions depicted in step D of scheme 1 could be carried out using the specialized conditions described herein or alternatively by applying the conditions or coupling reagents for amide bond construction described in Wallace, reference 95. Some specific nonlimiting examples are given in this application.

Additional procedures for synthesizing, modifying and attaching groups are contained in references 93-95 or described below.

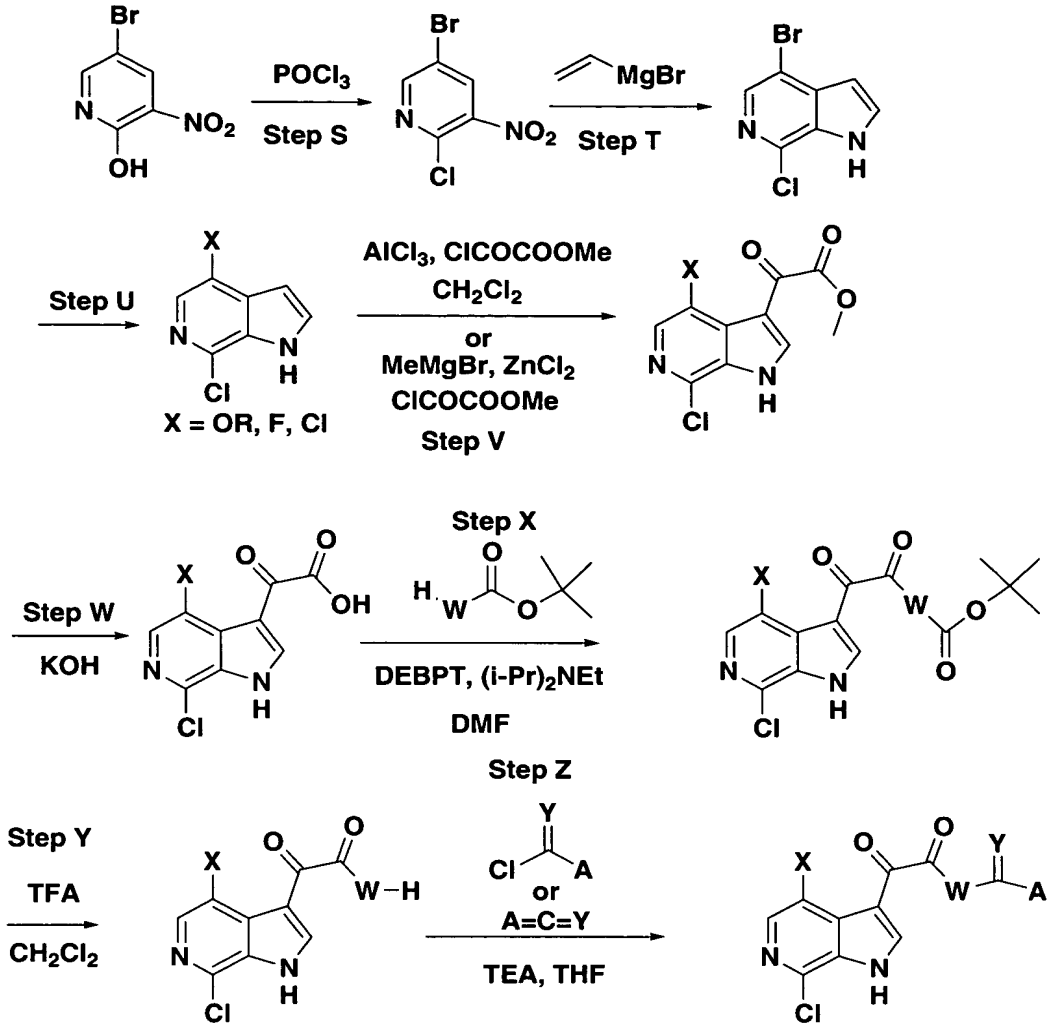
Scheme 3



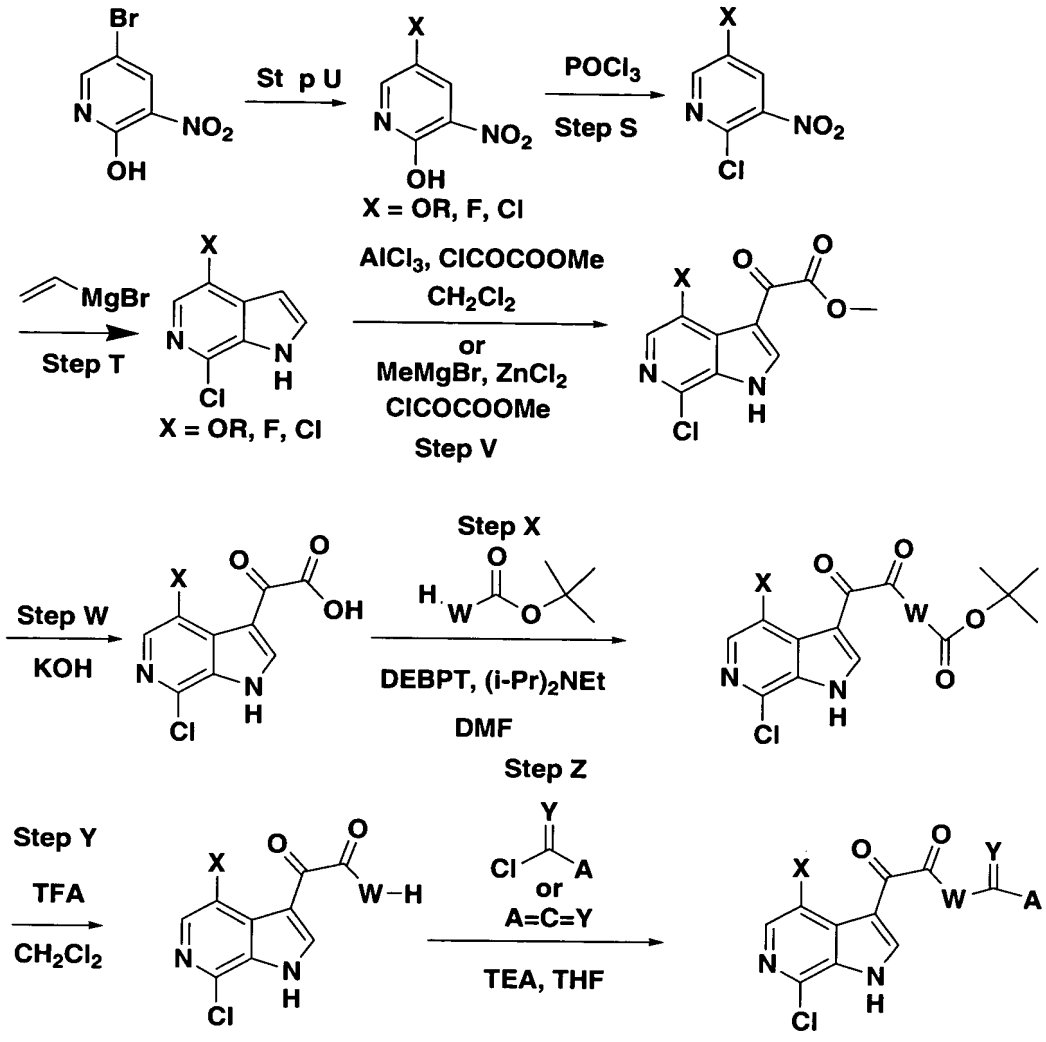
Schemes 1 and 3 provide more specific examples of the transformation previously described in Scheme A. Intermediates 9-15 are prepared by the methodologies as described for intermediates 1a-7a in Scheme 1. Scheme 4 is another embodiment of the transformations described in Schemes 1 and 3. Conversion of the phenol to the chloride (Step S, Scheme 4) may be accomplished according to the procedures described in Reimann, E.; Wichmann, P.; Hoefner, G.; Sci. Pharm. **1996**, *64(3)*, 637-646; and Katritzky, A.R.; Rachwal, S.; Smith, T.P.; Steel, P.J.; *J. Heterocycl. Chem.* **1995**, *32(3)*, 979-984. Step T of Scheme 4 can be carried out as described for Step A of Scheme 1. The bromo intermediate can then be converted into alkoxy, chloro, or fluoro intermediates as shown in Step U of Scheme 4. When step U is the conversion of the bromide into alkoxy derivatives, the conversion may be carried out by reacting the bromide with an excess of sodium methoxide in methanol with cuprous salts, such as copper I bromide, copper I iodide, and copper I cyanide. The reaction may be carried out at temperatures of between ambient and 175° C but most likely will be around 115°C or 100°C. The reaction may be run in a pressure vessel or sealed

tube to prevent escape of volatiles such as methanol. The preferred conditions utilize 3eq of sodium methoxide in methanol, CuBr as the reaction catalyst (0.2 to 3 equivalents with the preferred being 1 eq or less) , and a reaction temperature of 115° C. The reaction is carried out in a sealed tube or sealed reaction vessel. The conversion of the bromide into alkoxy derivatives may also be carried out according to procedures described in Palucki, M.; Wolfe, J.P.; Buchwald, S.L.; *J. Am. Chem. Soc.* **1997**, *119(14)*, 3395-3396; Yamato, T.; Komine, M.; Nagano, Y.; *Org. Prep. Proc. Int.* **1997**, *29(3)*, 300-303; Rychnovsky, S.D.; Hwang, K.; *J. Org. Chem.* **1994**, *59(18)*, 5414-5418. Conversion of the bromide to the fluoro derivative (Step U, Scheme 4) may be accomplished according to Antipin, I.S.; Vigalok, A.I.; Konovalov, A.I.; *Zh. Org. Khim.* **1991**, *27(7)*, 1577-1577; and Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H.; *Synlett.* **1992**, *4*, 345-346. Conversion of the bromide to the chloro derivative (Step U, Scheme 5) may be accomplished according to procedures described in Gilbert, E.J.; Van Vranken, D.L.; *J. Am. Chem. Soc.* **1996**, *118(23)*, 5500-5501; Mongin, F.; Mongin, O.; Trecourt, F.; Godard, A.; Queguiner, G.; *Tetrahedron Lett.* **1996**, *37(37)*, 6695-6698; and O'Connor, K.J.; Burrows, C.J.; *J. Org. Chem.* **1991**, *56(3)*, 1344-1346. Steps V, W, X, Y and Z of Scheme 4 are carried out according to the procedures previously described for Steps B, C, D, E and F of Scheme 1, respectively. The steps of Scheme 4 may be carried out in a different order as shown in Scheme 5 and Scheme 6.

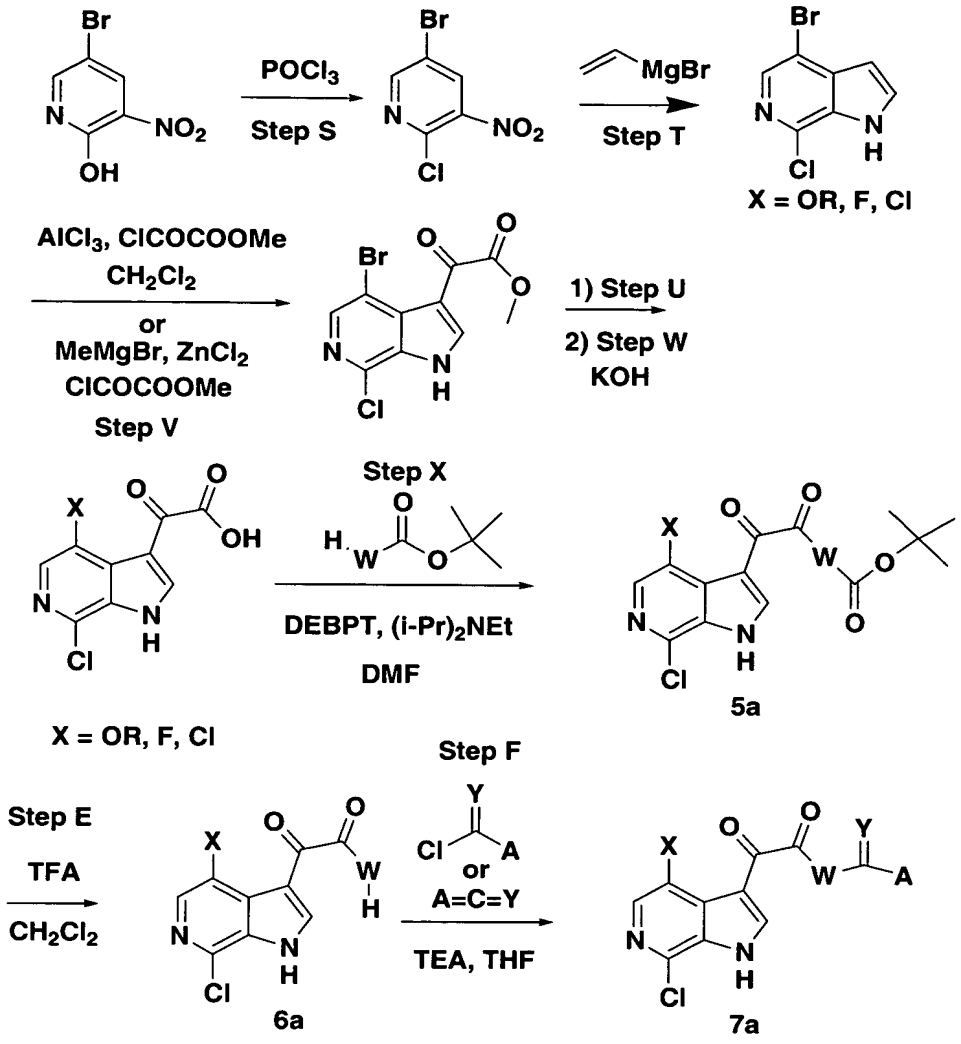
Scheme 4


Br
N
NO2
OH
POCl3
Step S
Br
N
NO2
Cl
MgBr
Step T
Br
N
N
H
Cl
Step U
X
N
N
H
Cl
X = OR, F, Cl
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
X
O
O
O
N
N
H
Cl
Step W
KOH
X
O
O
OH
N
N
H
Cl
Step X
H
W
O
O
DEBPT, (i-Pr)2NEt
DMF
X
O
O
W
O
O
N
N
H
Cl
Step Y
TFA
CH2Cl2
X
O
O
W–H
N
N
H
Cl
Step Z
Y
Cl
A
or
A=C=Y
TEA, THF
X
O
O
Y
W
A
N
N
H
Cl

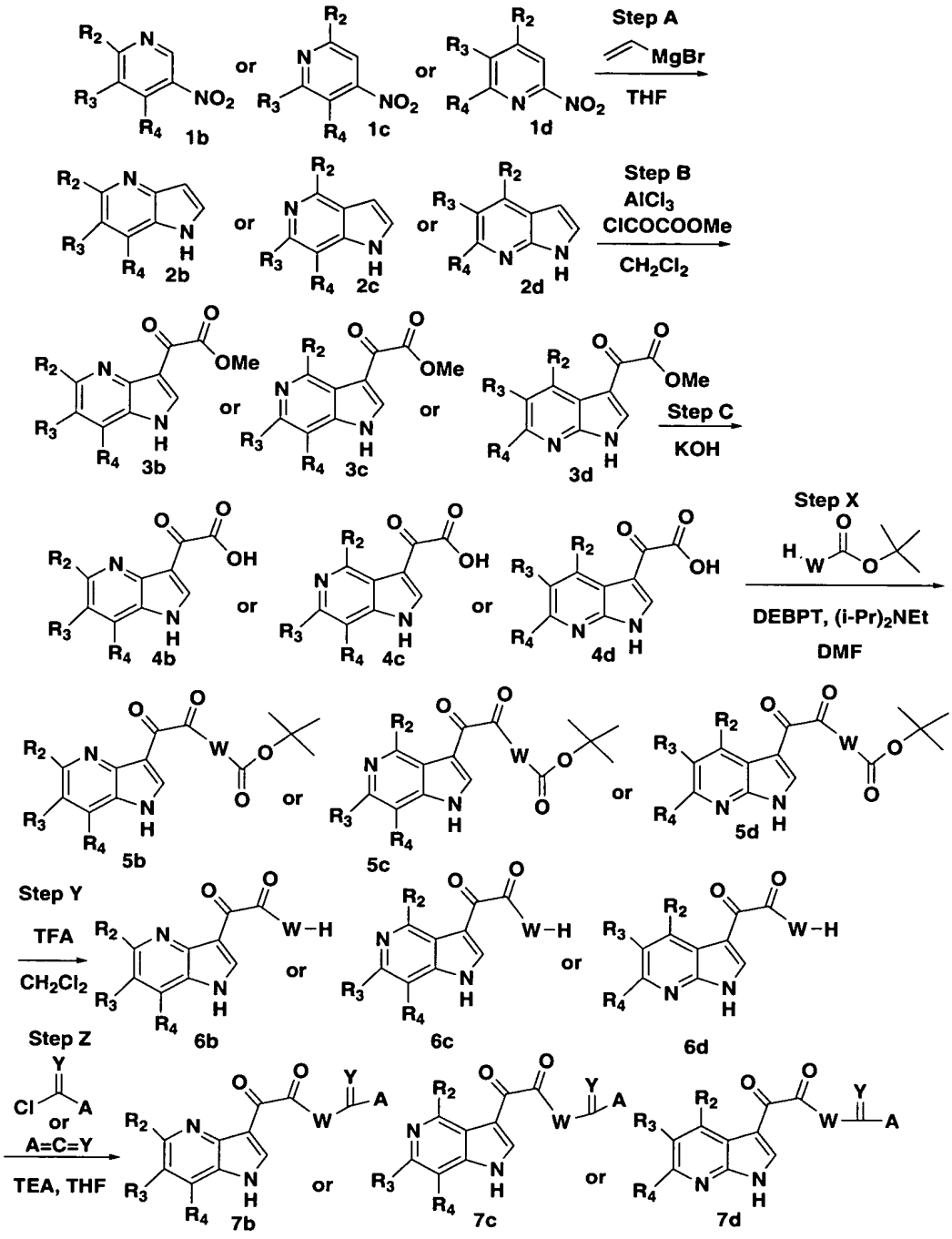
Scheme 5


Br
St p U
X
POCl3
Step S
NO2
OH
Cl
X = OR, F, Cl
MgBr
Step T
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
Step W
KOH
Step X
DEBPT, (i-Pr)2NEt
DMF
Step Z
Step Y
TFA
CH2Cl2
W–H
A=C=Y
TEA, THF

Scheme 6


Br
N
NO2
OH
POCl3
Step S
Cl
MgBr
Step T
H
X = OR, F, Cl
AlCl3, ClCOCOOMe
CH2Cl2
or
MeMgBr, ZnCl2
ClCOCOOMe
Step V
O
1) Step U
2) Step W
KOH
X
OH
Step X
W
DEBPT, (i-Pr)2NEt
DMF
5a
Step E
TFA
CH2Cl2
6a
Step F
Y
A
A=C=Y
TEA, THF
7a

Sch m 7

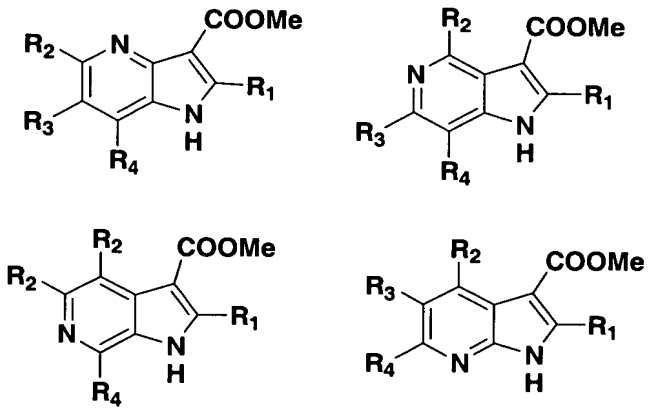


Scheme 7 shows the synthesis of 4-azaindole derivatives 2b-7b, 5-azaindole derivatives 2c-7c, and 7-azaindole derivatives 2d-7d. The methods used to synthesize 1b-5b, 1c-5c, and 1d-5d are the same methods described for the synthesis of 1a-5a as described in Scheme 1. It is understood, for the purposes of

Scheme 7, that 1b is used to synthesize 2b-5b, 1c provides 2c-5c and 1d provides 2d-5d.

The compounds where there is a single carbonyl between the azaindole and group W can be prepared by the method of Kelarev, V. I.; Gasanov, S. Sh.; Karakhanov, R. A.; Polivin, Yu. N.; Kuatbekova, K. P.; Panina, M. E.; *Zh. Org. Khim* **1992**, *28(12)*, 2561-2568. In this method azaindoles are reacted with trichloroacetyl chloride in pyridine and then subsequently with KOH in methanol to provide the 3-carbomethoxy azaindoles shown in Scheme 3 which can then be hydrolyzed to the acid and carried through sequence shown in the scheme to provide the compounds of Formula I wherein a single carbonyl links the azaindole moiety and group W.

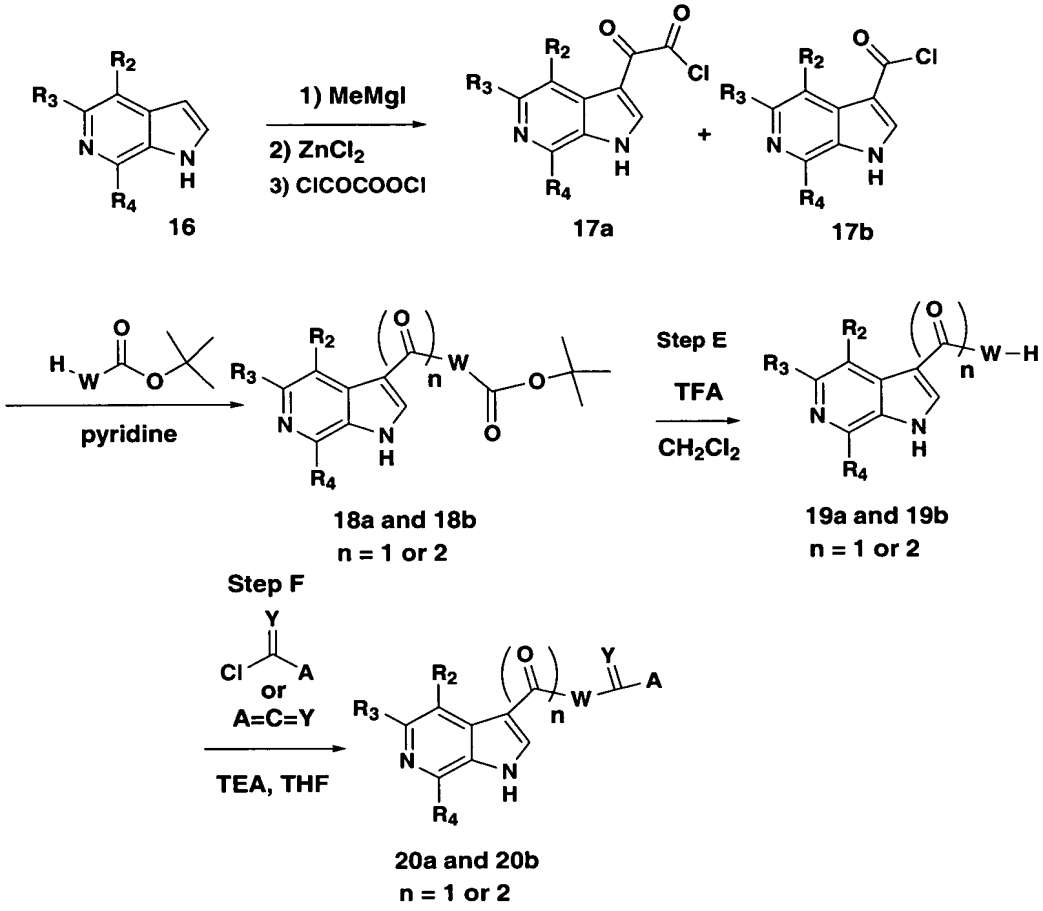
Scheme 8



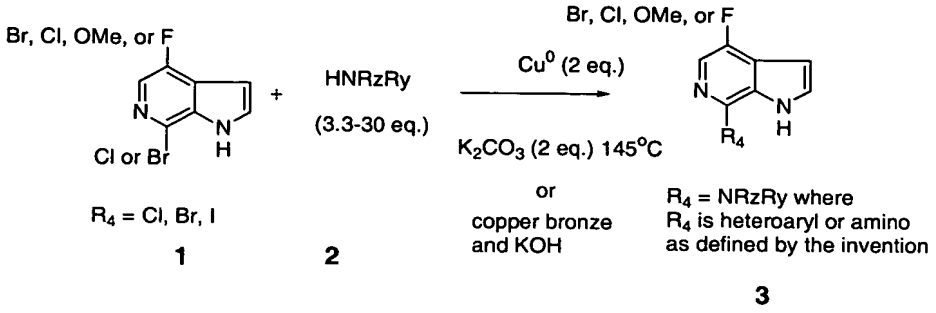
An alternative method for carrying out the sequence outlined in steps B-D (shown in Scheme 9) involves treating an azaindole, such as 16, obtained by procedures described in the literature or from commercial sources, with MeMgI and $ZnCl_2$, followed by the addition of ClCOCOCl (oxalyl chloride) in either THF or Et_2O to afford a mixture of a glyoxyl chloride azaindole, 17a, and an acyl chloride azaindole, 17b. The resulting mixture of glyoxyl chloride azaindole and acyl chloride azaindole is then coupled with mono-benzoylated piperazine derivatives under basic conditions to afford the products of step D as a mixture of

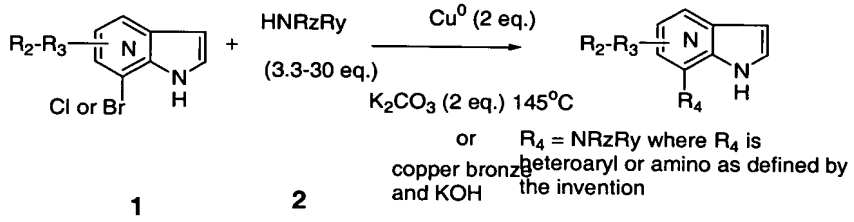
compounds, 18a and 18b, where either one or two carbonyl groups link the azaindole and group W. Separation via chromatographic methods which are well known in the art provides the pure 18a and 18b. Conversion of 18a and 18b to 20a and 20b can be done following steps E and F. This sequence is summarized in Scheme 9, below.

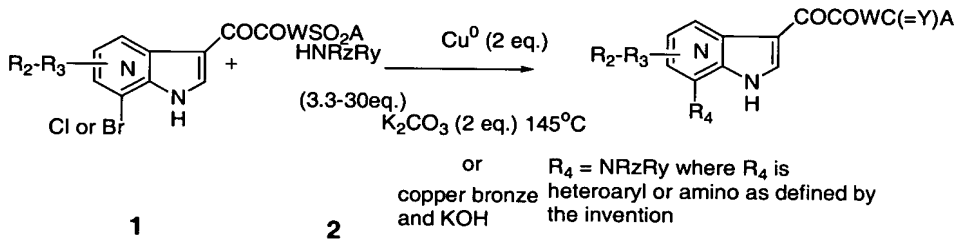
Scheme 9



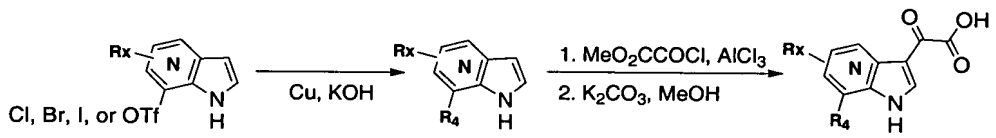
SCHEME 12





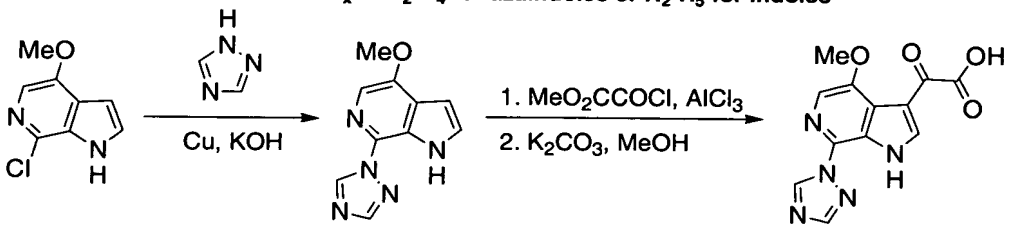


SCHEME 13



(R_4H is a heteroarylor amine with free N-H)

R_x = R_2-R_4 for azaindoles or R_2-R_5 for indoles



As shown in Schemes 12 and 13, a mixture of halo-indole or halo-azaindole intermediate, 1-2 equivalents of copper powder, with 1 equivalent preferred for the 4-F,6-azaindole series and 2 equivalents for the 4-methoxy,6-azaindole series; 1-2 equivalents of potassium carbonate, with 1 equivalent preferred for the 4-F,6-azaindole series and 2 equivalents for the 4-methoxy,6-azaindole series; and a 2-30 equivalents of the corresponding heterocyclic reagent, with 10 equivalents preferred; was heated at 135-160°C for 4 to 9 hours, with 5 hours at 160°C preferred for the 4-F,6-azaindole series and 7 hours at 135°C preferred for the 4-methoxy,6-azaindole series. The reaction mixture was cooled to room temperature and filtered through filter paper. The filtrate was diluted with methanol and purified either by preparative HPLC or silica gel. In many cases no chromatography is necessary, the product can be obtained by crystallization with methanol.

Alternatively, the installation of amines or N linked heteroaryls may be carried out by heating 1 to 40 equivalents of the appropriate amine and an equivalent of the appropriate aza indole chloride, bromide or iodide with copper bronze (from 0.1 to 10equivalents (preferably about 2 equivalents) and from 1 to 10 equivalents of finely pulverized potassium hydroxide (preferably about 2 equivalents). Temperatures of 120° to 200° may be employed with 140-160° generally preferred. For volatile starting materials a sealed reactor may be employed. The reaction is most commonly used when the halogen being displaced is at the 7-position of a 6-aza or 4-azaindole but the method can work in the 5-azaseries or when the halogen is at a different position (4-7 position possible) As shown above the reaction can be employed on azaindoles unsubstituted at position 3 or intermediates which contain the dicarbonyl or the intact dicarbonyl piperazine urea or thioureas contained in compounds of formula I.

Chemistry

All Liquid Chromatography (LC) data were recorded on a Shimadzu LC-10AS liquid chromatograph using a SPD-10AV UV-Vis detector with Mass Spectrometry (MS) data determined using a Micromass Platform for LC in electrospray mode.

LC/MS Method (i.e., compound identification)

Note: column A is used unless otherwise indicated in the preparation of intermediates or examples.

Column A: YMC ODS-A S7 3.0x50 mm column

Column B: PHX-LUNA C18 4.6x30 mm column

Column C: XTERRA ms C18 4.6x30 mm column

Column D: YMC ODS-A C18 4.6x30 mm column

Column E: YMC ODS-A C18 4.6x33 mm column

Column F: YMC C18 S5 4.6x50 mm column

Column G: XTERRA C18 S7 3.0x50 mm column

Gradient: 100% Solvent A / 0% Solvent B to 0% Solvent A / 100% Solvent

R_t in min.

Gradient time: 2 minutes

Hold time 1 minute

Flow rate: 5 mL/min

Detector Wavelength: 220 nm

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

Compounds purified by preparative HPLC were diluted in MeOH (1.2 mL) and purified using the following methods on a Shimadzu LC-10A automated preparative HPLC system or on a Shimadzu LC-8A automated preparative HPLC system with detector (SPD-10AV UV-VIS) wavelength and solvent systems (A and B) the same as above.

Preparative HPLC Method (i.e., compound purification)

Purification Method: Initial gradient (40% B, 60% A) ramp to final gradient (100% B, 0% A) over 20 minutes, hold for 3 minutes (100% B, 0% A)

Solvent A: 10% MeOH / 90% H_2O / 0.1% Trifluoroacetic Acid

Solvent B: 10% H_2O / 90% MeOH / 0.1% Trifluoroacetic Acid

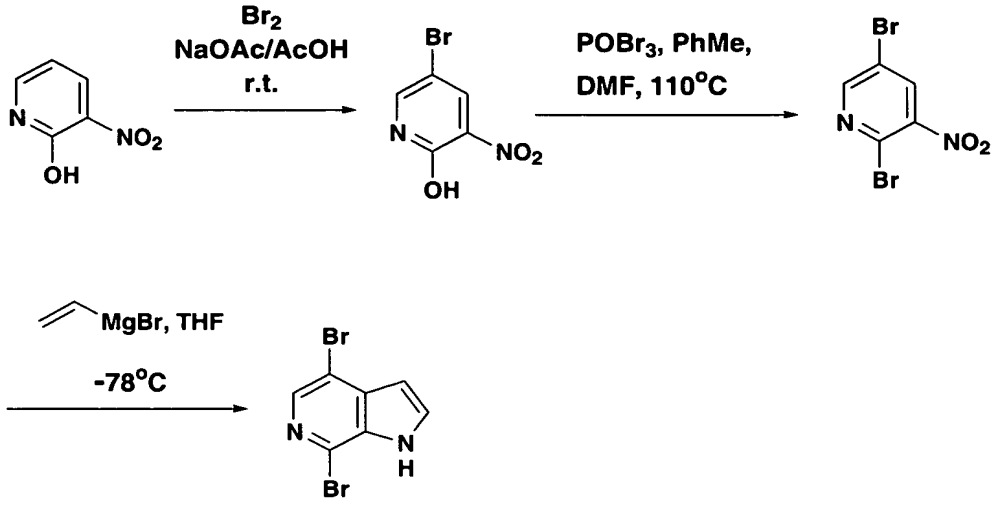
Column: YMC C18 S5 20x100 mm column

Detector Wavelength: 220 nm

General and Example Procedures excerpted from Analogous oxoacetyl piperazineamide applications

The procedures described references 93-95 and 106 are applicable example procedures for synthesizing the compounds of formula I in this application and the intermediates used for their synthesis. The following guidelines are illustrative but not limiting.

The general Bartoli (vinyl Magnesium bromide) methods for preparing functionalized indoles or azaindoles dexcribed in the applications can be utilized for preparing new indoles or azaindoles from the appropriate nitro aromatics or heteroaromatics for this application. For example, in PCT/US02/00455, the general procedure for preparing intermediate 2a (7-chloro-6-azaindole) from 2-chloro-3-nitro pyridine can be considered a general procedure illustrating conditions which can be used to prepare azaindoles for this application. This should be obvious since the same class of intermdiates are needed for both inventions. Similarly, the general procedure from the same application to prepare intermediate 3a, Methyl (7-chloro-6azaindol-3-yl) oxoacetate, provides experimental details for carrying our Step B of (Schemes 1-7 in this application) Similarly, the general procedure from the same application to prepare intermediate 4a (Potassium(7-chloro-6azaindol-3-yl) oxoacetate, provides an example of the general method for hydrolying oxoacteic esters (Step C of Schemes 1-1c, 3-7). General procedures for carrying out the same steps in the indole series are provided in references 93 and 95. An example Bartoli reaction preparation of a functionalized indole is given in the preparation of intermediate 1 of PCT/US01/20300 where the preparation of 4-fluoro-7-bromo-azaindole is described from 2-fluoro-5-bromonitrobenzene. The following Scheme provides an example of the preparation of 4,7-dibromo-6-azaindole via an extension of this methodology.

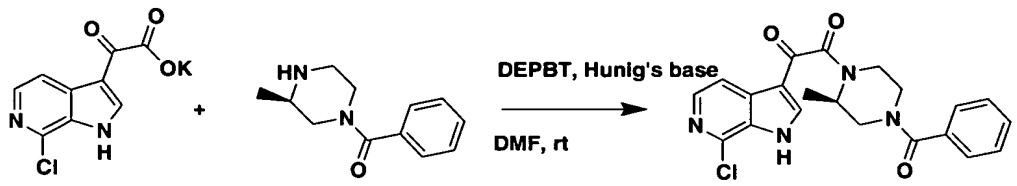


Subsequent procedures for the preparation of intermediates 2 and 3 describe procedures for adding the alkyl oxoacetate and then for ester hydrolysis to provide the carboxylate salt and then the carboxylic acid after acidification. Thus the chemistry described in the incoprorated previous applications for preparing azaindole and indole intermediates is obviously applicable since the desired compounds are the same.

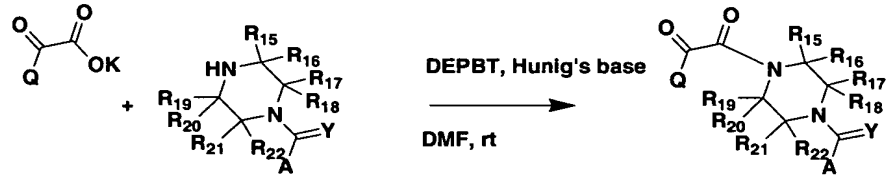
Procedures for carrying out the coupling of the indole or azaindole oxoacetic acids to piperazine amides are described in the references 93-95 and 106. These can also be used as procedures for preparing the piperazine sulfonyl ureas of this invention by taking the experimental procedures and substituting a piperazine sulfonyl urea or mon protected piperazine in place of the piperazine amide. This is possible because both groups have a free amine with relatively similar activity and since the other portions of both the piperazine benzamide and the piperizine sulfonyl urea are relatively unreactive to many conditions, they can be installed similarly. For example, the preparation of intermediate 4 of PCT/US01/20300 and the preparation of intermediate 5a of PCT/US02/00455 describe couplings of a piperazine benzamide or methyl piperazine benzamide to an indole or azaindole oxoacetic acid or carboxylate salt respectively. (The acid or salt can be used interchangeably). These same procedures can be used directly

for the preparation of the compounds of this invention by substituting the desired piperazine sulfonyl ureas for the piperazine amides utilized in earlier applications.

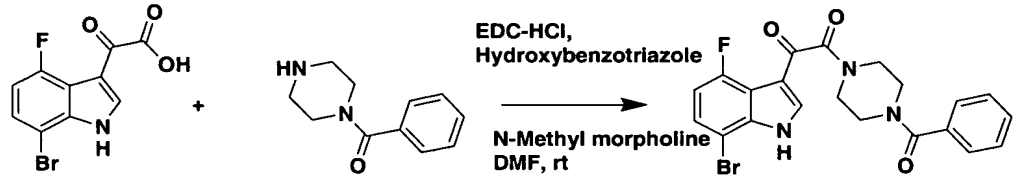
Preparation of Intermediate 5a from PCT/US02/00455



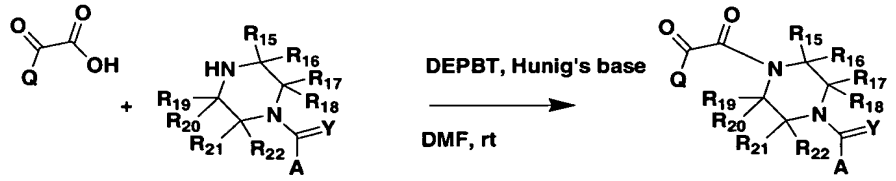
can be used as a procedure for



Preparation of Intermediate 4 from PCT/US01/20300



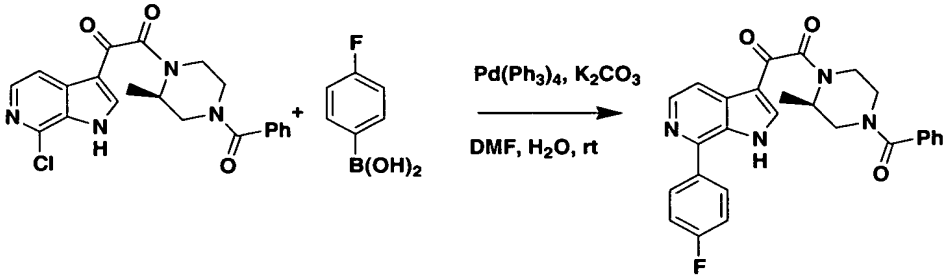
can be used as a procedure for



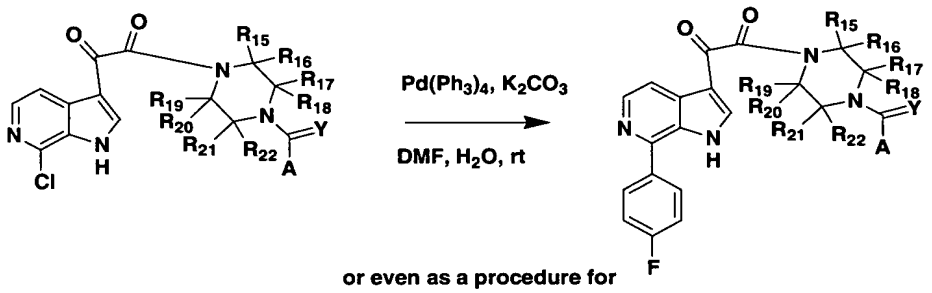
Once attached via a similar amide bond, both the piperazine benzamides and the piperazine sulfonyl urea moieties are relatively inert and thus reaction conditions used for functionalizing indoles or azaindoles in the presence of piperazine benzamides are useful for carrying out the same tranformations in the presence of the piperazine sulfonyl ureas. Thus the methods and transformations described in references 93-95 and 106 including the experimental procedures which describe methods to functionalize the indole or azaindole moiety in the piperazine amide series are generally applicable for construction and

functionalization of the piperazine sulfonyl ureas of this invention. These same applications describe general methods and specific preparations for obtaining stannane and boronic acid reagents used for synthesizing the compounds of formula I.

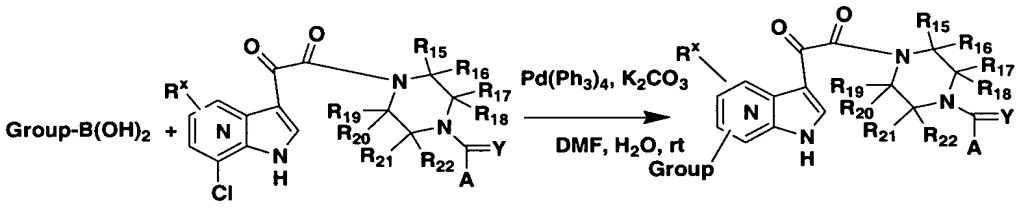
Preparation of Example 1 from PCT/US02/00455
Typical Boron /palladium coupling procedure



can be used as a procedure for



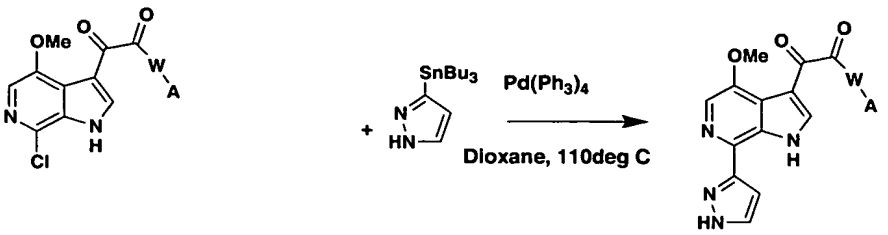
or even as a procedure for



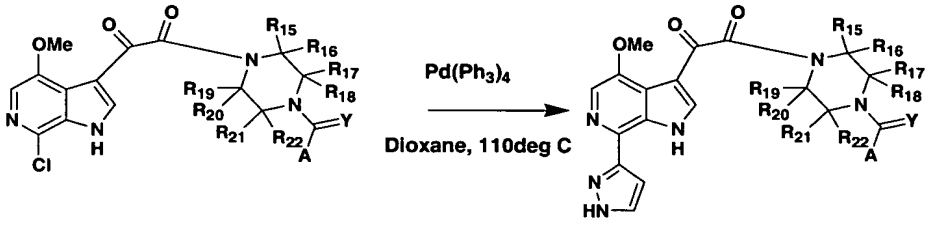
functionalized indole or azaindole

where R^x is as described for Scheme 7

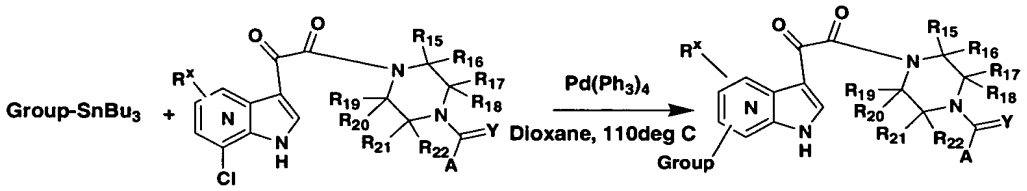
Preparati n of Example 39 from PCT/US02/00455
An example of the typical stannane /palladium coupling procedure



can be used as a procedure for



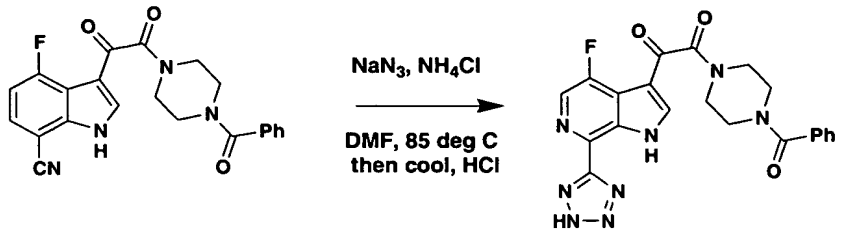
or even as a procedure for



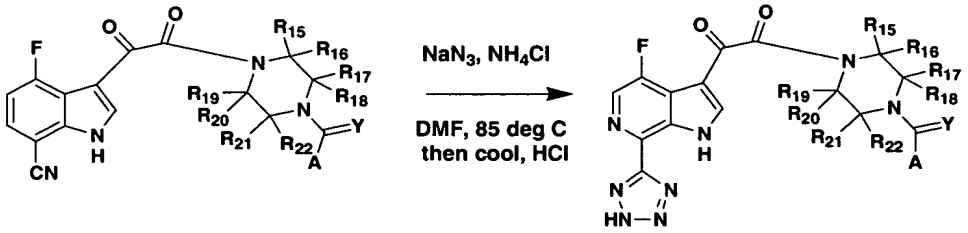
functionalized Indole or azaIndole

where R^x is as described for Scheme 7

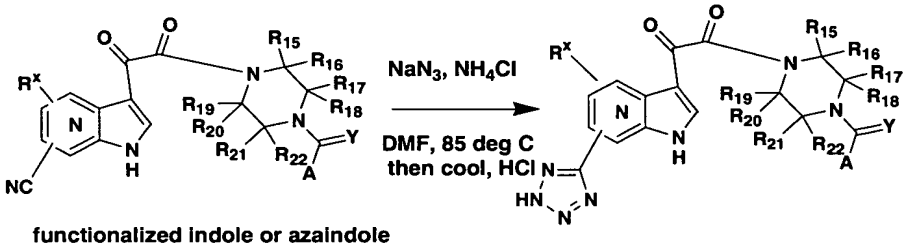
Preparation of Exampl 20 fr m PCT/US01/20300
An example to sh w h w functi nalizati n procedures of oxoacetyl piperazin benzamides can b us d t carry ut similar tranf rmati ns in th corr sp nding piperidine alken s



can be used as a procedure for



or even as a procedure for



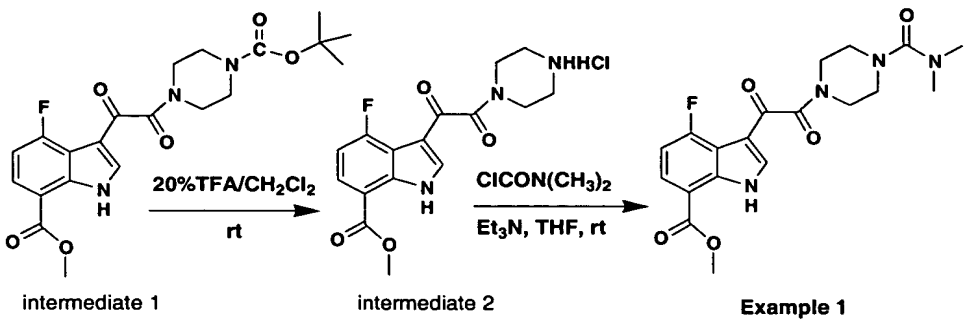
functionalized indole or azaindole

where R^x is as described for Scheme 7

Preparation of intermediates and examples:

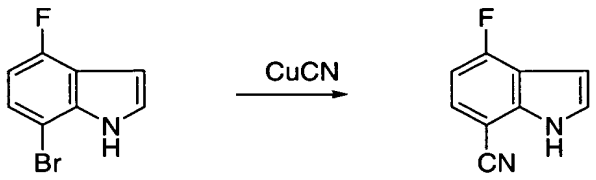
All starting materials, unless otherwise indicated can be purchased from commercial sources. Methods are given for the preparation of all intermediates.

Example 1:



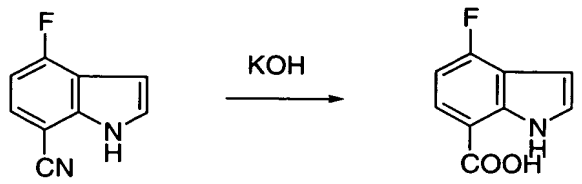
Preparation of intermediate 1. Intermediate 1 was prepared according to procedures described in Wallace, O. B. et al. PCT int. appl. WO0204440, and as described in Steps A-D below.

STEP A



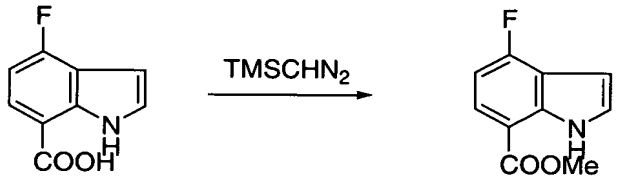
A mixture of 4-fluoro-7-bromoindole (600 mg, 2.8 mmol) and CuCN (1.004 g, 11.2 mmol) in DMF (4 ml) was refluxed for 16 hours. After cooling to room temperature, the reaction mixture was poured into a solution of ammonia in MeOH (30 ml, sat.) and the residue removed by filtration. The filtrate was added to a mixture of water (20 ml)/ammonia (20 ml, sat. aq.) and extracted with EtOAc/Ether (1/1) until TLC analysis showed no product in the aqueous phase. The combined organic extracts were washed with brine (2 x 200 ml) and water (200 ml), dried ($MgSO_4$); evaporation *in vacuo* gave 4-fluoro-7-cyanoindole as a tan yellow solid (310 mg, 69%).

STEP B



To a solution of KOH (13.04 g, 0.232 mol) in 14% H_2O/EtOH (50 ml) was added 4-fluoro-7-cyanoindole (900 mg, 5.60 mmol). The resulting mixture was refluxed for 12 hours, slowly cooled to room temperature, and concentrated *in vacuo* to about 30 ml. The residue was acidified to pH 2 with HCl (~5.5 *N* aq.). The precipitate was filtered, washed with excess of water, and dried under high vacuum to afford 4-fluoro-7-carboxyindole as a white solid (100% conversion). The material was used without further purification.

STEP C



To a suspension of 4-fluoro-7-carboxyindole in a mixture of MeOH (18 ml)/PhH (62 ml) was added (trimethylsilyl)diazomethane (8.8 ml, 17.6 mmol, 2 *M* in hexane). The resulting mixture was stirred at room temperature for 30 min., quenched with excess acetic acid and evaporated *in vacuo*. The crude oily material was purified by flash chromatography using a gradient elution (Hexane to 10% EtOAc/Hexane) to afford 4-fluoro-7-carbomethoxy indole as a white solid (1.04 g, 83% two steps).

STEP D

Oxalyl chloride (1.2 eq.) was added dropwise to a solution of 4-fluoro-7-carbomethoxy indole (1 eq.) prepared as described above, in dry THF at 0°C. After 5 min., the cool bath was removed and the reaction was allowed to warm to rt and stirred until completion determined by LCMS. The mixture was then concentrated under reduced pressure to provide the crude oxo acetyl chloride. Triethylamine (8.88 mmol, 1.23 mL) and 1-Boc piperazine (7.4 mmol, 1.38 g) was added to a solution of the crude 3-oxoacetyl chloride of 4-fluoro-7-carbomethoxy indole (7.4 mmol) in THF (70 mL) and the mixture was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added and then the mixture was extracted with methylene chloride (3 x 100 mL). The combined organic extracts were dried over sodium sulfate to afford a crude containing intermediate 1. This crude intermediate 1 was used without further purification in the next step. MS (ESI^+): $333(M+H)^+$.

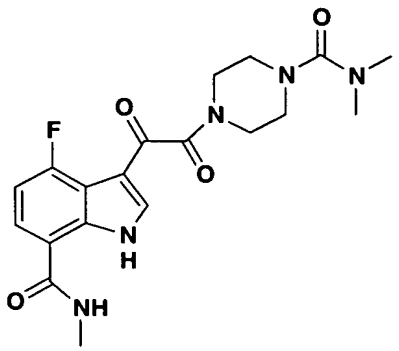
Preparation of intermediate 2

Intermediate 1 (80 mg, 0.18 mmol) was treated with a solution of 20%TFA in methylene chloride (2 mL) at room temperature. After stirring for 3h, the resulting mixture was concentrated and dried in vacuo to afford intermediate 2 which was used in next step without further purification. MS (ESI^+): 441 $(M+H)^+$.

Example 1

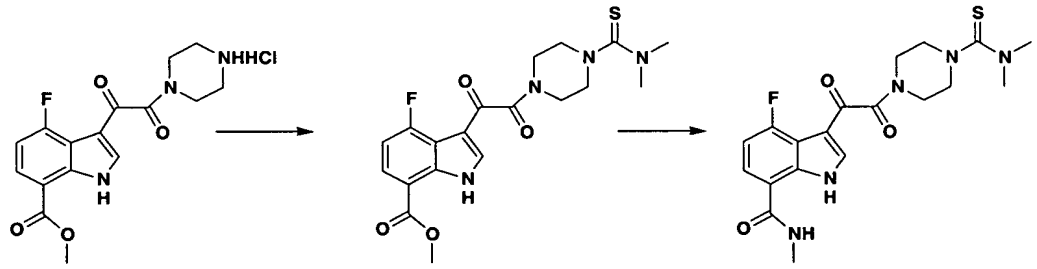
A THF (1ml) solution of intermediate 2 (0.30 mmol) was treated with triethylamine (125 μl, 0.90 mmol) followed by dimethylcarbamoyl chloride (55 μl, 0.60 mmol) at room temperature. The reaction was stirred for 16h, then concentrated in a rotoevaporator to afford example 1 as a pale yellow film. ^{1}NMR (300 MHz, $CDCl_3$): 8.11 (d, 1H, J = 3.0 Hz); 7.97 -7.92 (m, 1H); 7.03 - 6.97 (m, 1H); 3.98 (s, 3H), 3.77 (m, 2H); 3.54 (m, 2H); 3.35 (m, 2H); 3.26 (m, 2H); 2.85 (s, 6H). MS (ESI^+): 405 $(M+H)^+$.

Example 2



Example 1 (0.15 mmol) was treated with a solution of 40% methylamine in water (1 mL) and the mixture was stirred at room temperature for 3h, then concentrated in rotoevaporator and chromatographed on silica gel to afford the title compound as a white solid (9.5 mg, 16% from intermediate 1). ^{1}NMR (300 MHz, $CDCl_3$): 8.09 (d, 1H, J = 3.0 Hz); 7.42 -7.39 (m, 1H); 6.97 - 6.91 (m, 1H); 6.55 - 6.45 (bs, 1H); 3.77 (m, 2H); 3.54 (m, 2H); 3.36 (m, 2H); 3.26 (m, 2H); 3.04 (d, 3H, J = 5.0 Hz); 2.85 (s, 6H). MS (ESI$^+$): 404 $(M+H)^+$.

Example 3



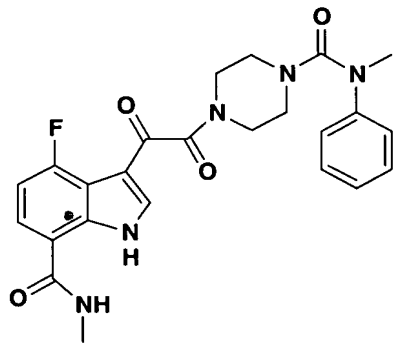
Example 3 was prepared in two steps from intermediate 2:

Step 1: Acylation: A THF (1ml) solution of intermediate 2 (0.30 mmol) was treated with triethylamine (125 μl, 0.90 mmol) followed by dimethylthiocarbamoyl chloride (81 mg, 0.60 mmol) at room temperature. The

reaction was stirred for 48h, then concentrated in rotoevaporator to afford intermediate 3 which was used in next step without further purification.

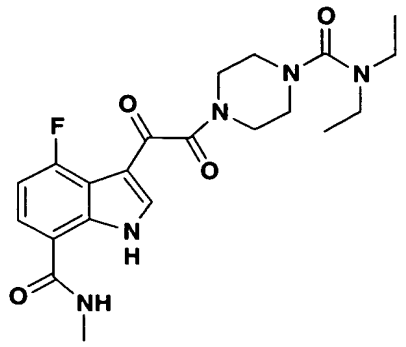
Step 2: Aminolysis: The crude residue of intermediate 3 from the previous reaction was dissolved in 1mL of MeOH and treated with 2 mL of a 40% solution of methylamine in water. The reaction mixture was stirred at rt for 18h, then it was concentrated to dryness and chromatographed in silica gel to afford the title compound example 3 as a white solid. ^{1}NMR (300 MHz, $CDCl_3$): 8.11 (d, 1H, *J* = 3.0 Hz); 7.43 -7.40 (m, 1H); 6.99 - 6.95 (m, 1H); 6.35 (bs, 1H); 3.83 (m, 2H); 3.62-3.52 (m, 6H); 3.05 (s, 6H); 3.05 (d, 3H, *J* = 5.0 Hz). MS (ESI$^+$): 421 $(M+H)^+$.

Example 4



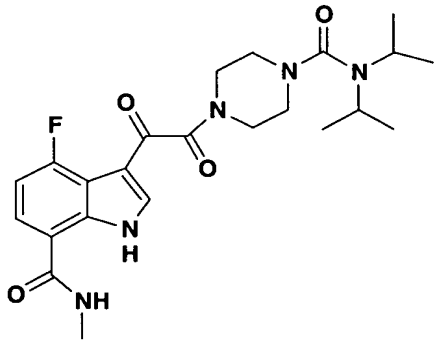
Example 4 was prepared from intermediate 2 following the procedure described for preparation example 2, using methyl,phenyl carbamoyl chloride as the acylating agent. ^{1}NMR (300 MHz, MeOH): 7.45 -7.42 (m, 3H); 7.39 – 7.24 (m, 3H); 7.13 (m, 1H), 5.56 (bs, 1H); 3.30 (m, 2H); 3.21 (m, 2H); 3.18 (m, 2H); 2.98 (m, 2H); 2.66 (s, 6H);. MS (ESI$^+$): 466 $(M+H)^+$.

Example 5



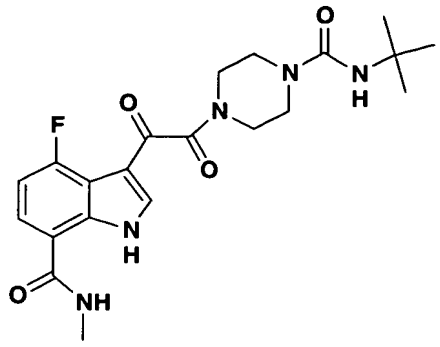
Example 5 was prepared from intermediate 2 following the procedure described for preparation example 2, using diethylcarbamoyl chloride as the acylating agent. ^{1}NMR (500 MHz, $CDCl_3$): 8.04 (d, 1H, J = 3.0 Hz); 7.40 -7.39 (m, 1H); 6.91 - 6.87 (m, 1H); 6.75 (bs, 1H); 3.76 (m, 2H); 3.52 (m, 2H); 3.33 (m, 2H); 3.24-3.02 (m, 6H); 3.01 (d, 3H, J = 5.0 Hz); 1.12 (m, 6H). MS (ESI^+): 432 $(M+H)^+$.

Example 6



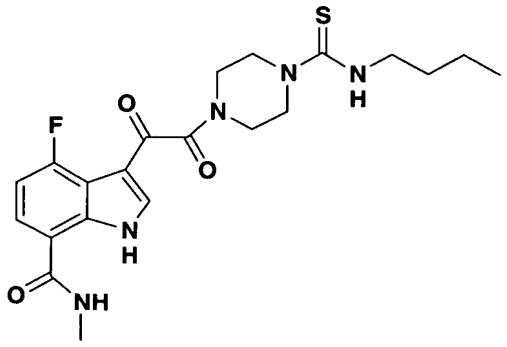
Example 6 was prepared from intermediate 2 following the procedure described for preparation example 2, using diisopropyl carbamoyl chloride as the acylating agent. ^{1}NMR (500 MHz, $CDCl_3$): 8.08 (d, 1H, J = 3.0 Hz); 7.42 -7.39 (m, 1H); 6.97 - 6.91 (m, 1H); 6.55 - 6.45 (bs, 1H); 3.77 (m, 2H); 3.63 (m, 2H); 3.54 (m, 2H); 3.22 (m, 2H); 3.12 (m, 2H); 3.04 (d, 3H, J = 5.0 Hz); 1.26 (d, 6H, J = 6.5 Hz). MS (ESI^+): 460 $(M+H)^+$.

Example 7



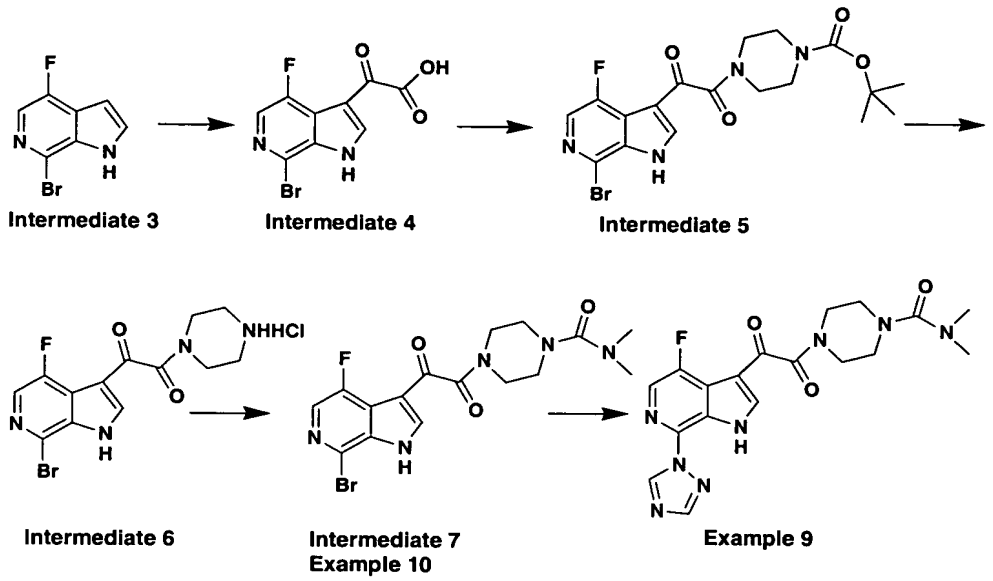
Example 7 was prepared from intermediate 2 following the procedure described for preparation example 2, using tertbutyl isocyanate as the acylating agent. ^{1}NMR (500 MHz, $CDCl_3$): 8.11 (d, 1H, J = 3.0 Hz); 7.40 -7.37 (m, 1H); 6.97 - 6.93 (m, 1H); 6.55 - 6.45 (bs, 1H); 3.77 (m, 2H); 3.54 (m, 2H); 3.49 (m, 2H); 3.39 (m, 2H); 3.05 (d, 3H, J = 5.0 Hz); 1.35 (s, 9H).
MS (ESI$^+$): 432 $(M+H)^+$.

Example 8



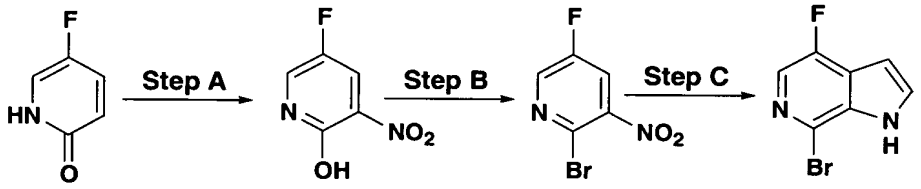
Example 8 was prepared from intermediate 2 following the procedure described for preparation example 2, using butyl isothiocyanate as the acylating agent. ^{1}NMR (500 MHz, $CDCl_3$): 8.10 (d, 1H, J = 3.0 Hz); 7.42 -7.39 (m, 1H); 6.97 - 6.91 (m, 1H); 6.55 - 6.45 (bs, 1H); 3.93 (m, 2H); 3.89 (m, 2H); 3.81 (m, 2H); 3.66 (m, 4H); 3.06 (d, 3H, J = 5.0 Hz); 1.30-1.45 (m, 4H); 0.85-0.93 (m, 3H). MS (ESI$^+$): 448 $(M+H)^+$.

Example 9



Preparation of intermediate 3

Intermediate 3, 4-fluoro-7-bromo-6-azaindole, was prepared according to the following scheme:



A) fuming HNO_3, H_2SO_4;

B) $POBr_3$/DMF, 110°C;

C) vinylmagnesium bromide, THF, -78°C ~ -20°C

Intermediate 3 was isolated as a brownish solid. MS *m/z*: $(M+H)^+$ calcd for $C_7H_5BrFN_2$: 214.96; found 214.97. HPLC retention time: 1.28 minutes (column G).

Preparation of intermediate 4

To a solution of 1-ethyl-3-methyl imidazolium chloride (2.7g, 18.6mmol) and aluminum chloride (7.5g, 55.8mmol) was added intermediate 3 (2.0g, 9.3mmol) followed by slow addition of ethyloxalylacetate (2.1ml, 18.6mmol) at room temperature. The reaction was then stirred at room temperature for 20h, and quenched by slow addition of ice water (20mL). A light brown solid precipitated out and collected by filtration and dried in air to provide of intermediate 4 (2.2g, 82%). LC/MS: (ES^+) m/z $(M+H)^+$ = 289. Rt = 0.85min.

Preparation of intermediate 5

A mixture of intermediate 4 (574mg, 2.0mmol), 1-Boc-piperazine (1.1g, 6.0mmol), HOBt Hydrate (612mg, 4.0mmol), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (764mg, 4.0mmol) and N-methyl-morpholine (1.3mL, 12mmol) in DMF (15 mL) was stirred for 30h at room temperature. The reaction was quenched with water (20mL). The resulting mixture was extracted with ethylacetate (3 x 30mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was chromatographed to afford intermediate 5 as a white powder (667mg, 73%). ^1H NMR (300MHz, $CDCl_3$): 9.34 (bs, 1H); 8.26-8.25 (m, 1H); 8.11-8.10 (m, 1H); 3.74-3.50 (m, 8H); 1.57 (s, 9H). LC/MS: (ES^+) m/z $(M+H)^+$ = 457. Rt = 1.43min.

Preparation of intermediate 6

Intermediate 5 (417mg, 0.92mmol) was treated with 4N HCl in dioxane (5mL, 20mmol). After stirring for 15h, the reaction mixture was concentrated on rotoevaporator and dried in vacuo. The resulting light yellow powder was characterized by LCMS and carried to the next step without purification. LC/MS: (ES^+) m/z $(M+H)^+$ = 357. Rt = 0.55min.

Preparation of intermediate 7

Intermediate 6 (100mg, 0.26mmol) was dissolved in acetonitrile (1.5mL) and treated with dimethylcarbamoyl chloride (48ul, 0.52mmol) followed by triethylamine (100ul, 0.78mmol). The reaction was stirred for 15h at room temperature. The solid was filtered out. The filtrate was concentrated and dried in vacuo to provide intermediate 7 as a yellow solid which was used in the next step without further purification. ^{1}H NMR (300MHz, $CDCl_3$): 10.9 (bs, 1H); 8.27-8.26 (m, 1H); 8.08-8.07 (m, 1H); 3.75-3.11 (m, 8H); 2.85 (s, 6H). LC/MS: (ES^+) m/z $(M+H)^+$ = 428. Rt = 0.96min.

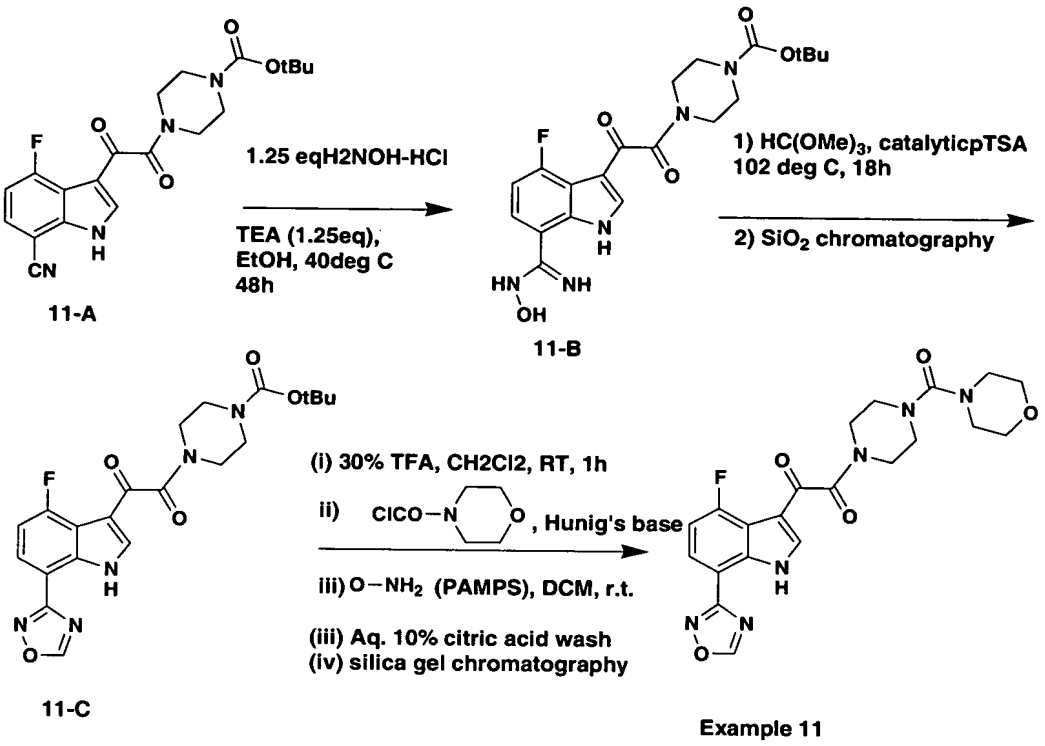
Preparation of Compound Example 9

A mixture of intermediate 7 (100mg, 0.22mmol), 1,2,4-triazole (455mg, 6.6mmol), copper powder (14mg, 0.22mmol) and potassium carbonate (30mg, 0.22mmol) was heated at 160°C for 7h in a sealed tube. The reaction was cooled to room temperature and filtered through filter paper. The filtrate was diluted with methanol and purified by preparative HPLC to provide the title compound. ^{1}H NMR (500MHz, $CDCl_3$): 9.30 (s, 1H); 8.32-8.31 (m, 1H); 8.24 (s, 1H); 8.10-8.09 (m, 1H); 3.79-3.29 (m, 8H)); 3.98-3.45 (m, 8H); 2.87 (s, 6H). LC/MS: (ES+) m/z $(M+H)^+$ = 415. Rt = 1.01min.

Preparation of Examples 11-14

The respective Boc piperazine amides were prepared as described in references 93 and 95. Standard TFA deprotection provided the corresponding QC(O)C(O)W-H (or Z-W-H) for these three examples. Coupling with morpholine as described in Scheme A of this application provided the compounds of Examples 11-14. More details and a separate description of the methods used for characterization of these compounds follow.

Preparation of Example 11

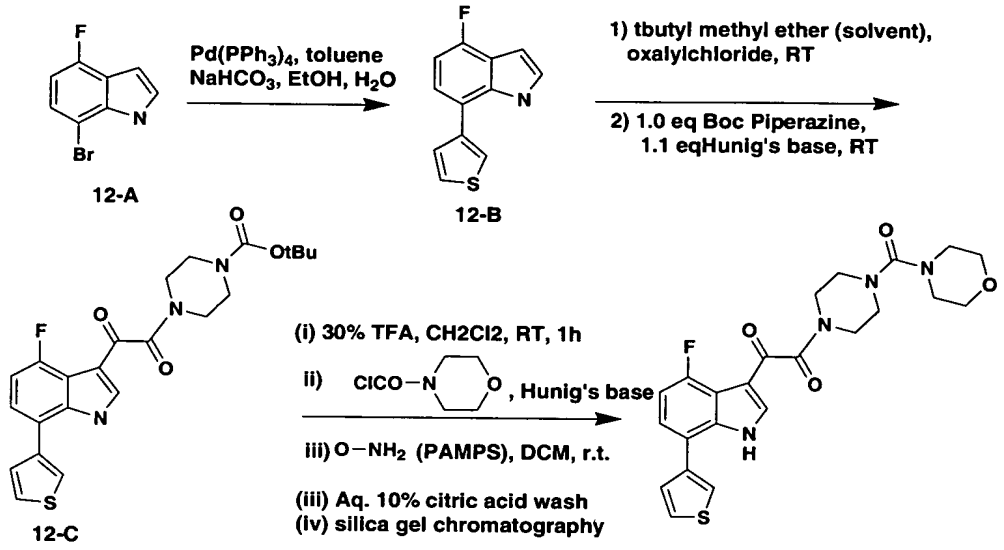


Intermediates 11-A, 11-B, and 11-C were prepared as described in the scheme above which is using the methods previously described references 93 and 95. Standard TFA deprotection and standard urea formation could be used to prepare the desired example. A more detailed description of the actual procedure used to convert 11-C to Example 11 is described below.

A well of a standard 96 well plate was loaded with 1mL of dichloromethane then the corresponding piperazine and then morpholine 4-carbonyl chloride (1.1 eq, 0.0470 to 0.0532 mmol) were then added. Next 1.1eqs of Hunig's base (diisopropylethylamine) were added and the plate shaken overnight at ambient temperature. Two equivalents of PAMPS (n-propylaminomethylolystyrene, 1/mmol per gram) were added for each equivalent of acid chloride and the reaction mixture shaken overnight. The wells were agitated by adding, pipetting, and re-adding 0.5mL 10% aq citric acid about ten times. The contents of the well was passed through anhydrous MgSO4, and the

products either used and purified by passage over SiO2 using ~9:1 ethylacetate: methanol or gradient.

Preparation of Examples 12



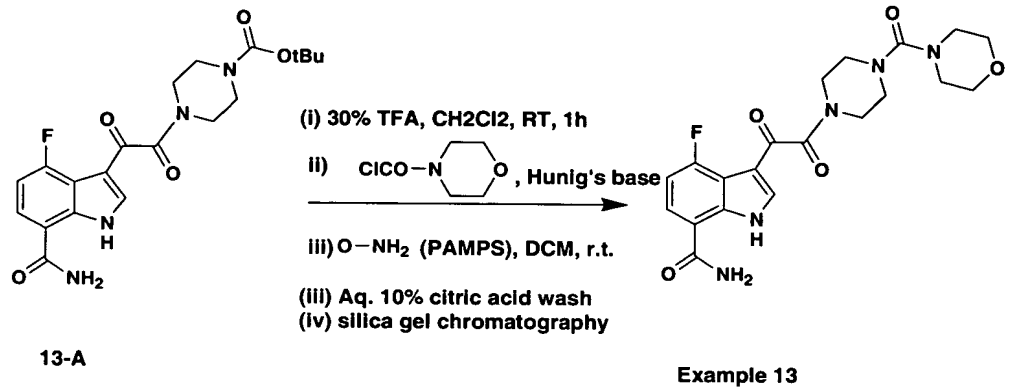
Example 12

Intermediates 12-A, 12-B, and 12-C were prepared as described in the scheme above which is using the methods previously described in references 93 and 95. Standard TFA deprotection and standard urea formation could be used to prepare the desired example. A more detailed description of the actual procedure used to convert 12-C to Example 12 is described below.

A well of a standard 96 well plate was loaded with 1mL of dichloromethane then the corresponding piperazine and then morpholine 4-carbonyl chloride (1.1 eq, 0.0470 to 0.0532 mmol) were then added. Next 1.1eqs of Hunig's base (diisopropylethylamine) were added and the plate shaken overnight at ambient temperature. Two equivalents of PAMPS (n-propylaminomethylolystyrene, 1/mmol per gram) were added for each equivalent of acid chloride and the reaction mixture shaken overnight. The wells were agitated by adding, pipetting, and re-adding 0.5mL 10% aq citric acid about ten times. The contents of the well was passed through anhydrous MgSO4, and the

products either used and purified by passage over SiO2 using ~9:1 ethylacetate: methanol or gradient.

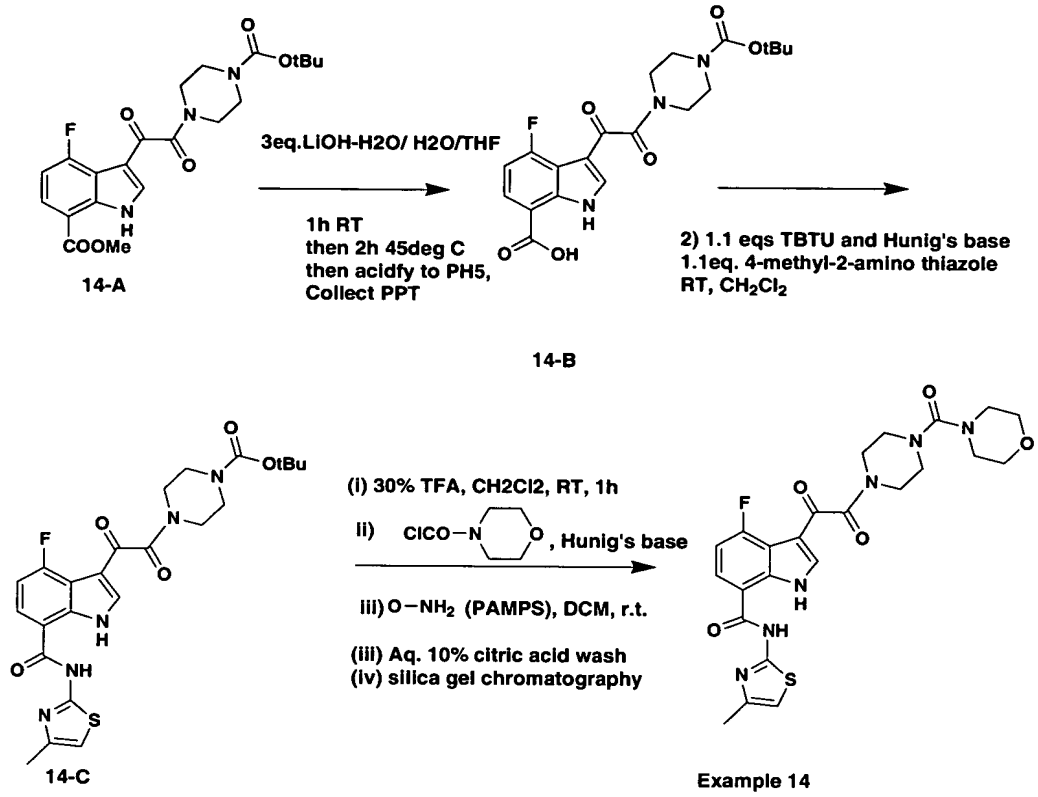
Preparation of Example 13



Intermediate 13-A was prepared as described in the scheme above which is using the methods previously described references 93 and 95. Standard TFA deprotection and standard urea formation could be used to prepare the desired example. A more detailed description of the actual procedure used to convert 13-A to Example 13 is described below.

A well of a standard 96 well plate was loaded with 1mL of dichloromethane then the corresponding piperazine and then morpholine 4-carbonyl chloride (1.1 eq, 0.0470 to 0.0532 mmol) were then added. Next 1.1eqs of Hunig's base (diisopropylethylamine) were added and the plate shaken overnight at ambient temperature. Two equivalents of PAMPS (n-propylaminomethylolystyrene, 1/mmol per gram) were added for each equivalent of acid chloride and the reaction mixture shaken overnight. The wells were agitated by adding, pipetting, and re-adding 0.5mL 10% aq citric acid about ten times. The contents of the well was passed through anhydrous MgSO4, and the products either used and purified by passage over SiO2 using ~9:1 ethylacetate: methanol or gradient.

Preparation of Examples 14



Intermediates 14-A, 14-B, and 14-C were prepared as described in the scheme above which is using the methods previously described references 93 and 95. Standard TFA deprotection and standard urea formation could be used to prepare the desired example. A more detailed description of the actual procedure used to convert 14-C to Example 14 is described below.

A well of a standard 96 well plate was loaded with 1mL of dichloromethane then the corresponding piperazine and then morpholine 4-carbonyl chloride (1.1 eq, 0.0470 to 0.0532 mmol) were then added. Next 1.1eqs of Hunig's base (diisopropylethylamine) were added and the plate shaken overnight at ambient temperature. Two equivalents of PAMPS (n-propylaminomethylolystyrene, 1/mmol per gram) were added for each equivalent of acid chloride and the reaction mixture shaken overnight. The wells were agitated by adding, pipetting, and re-adding 0.5mL 10% aq citric acid about ten times. The contents of the well was passed through anhydrous MgSO4, and the

products either used and purified by passage over SiO2 using ~9:1 ethylacetate: methanol or gradient.

Characterization data for examples 11-14

The HPLC methods used for examples 11-14 are described below and therefore for these examples the general methods described above are superceded by these procedures.

10 minute HPLC method for examples 11-14

1. Apparatus and Reagents

1.1 Common Apparatus

0.1% Trifluoroacetic acid (aq) – Mobile phase "A"

0.1% Trifluoroacetic acid (acetonitrile) – Mobile phase "B"

Phenomenex Luna C8 (2) 100 x 2.0 mm, 3µm column

Waters Millennium^{32} ™ Chromatography Data System (V3.2 or better)

1.2 Instrumentation

Waters 2790 LC system ("LC19"), comprising:

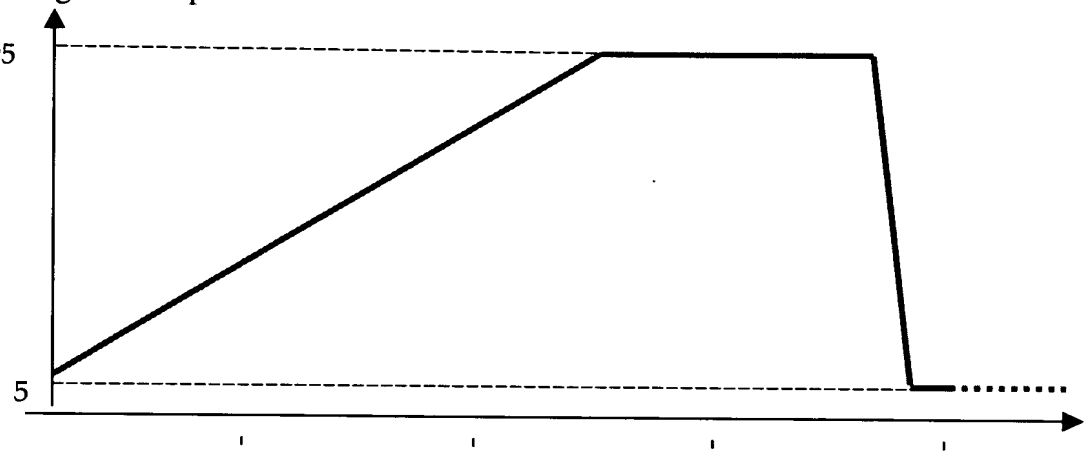
Waters 2790 Separations Module

Waters 2487 Dual Wavelength Absorbance Detector – wavelength set at 215nm.

2. Instrument Parameters

LC Conditions

% Organic composition



The dashed line represents re-equilibration. Overall run time is ~13.5 minutes, the mass spectrometer and Millennium[32] captures the first 10 minutes of the run.

Flow rate = 0.3 ml/min

Run time = 13.5 minutes

Gradient:	Time (mins)	% Organic
	0.00	5
	6.30	95
	9.50	95
	9.70	5
	13.5	5

3. Integration and Reporting

Data is integrated using Millennium and reported via the Millennium software.

2.5 Minute HPLC method for Examples 41 and 42

4. Apparatus and Reagents

4.1 Common Apparatus

0.1% Trifluoroacetic acid (aq) – Mobile phase "A"

0.1% Trifluoroacetic acid (acetonitrile) – Mobile phase "B"

Hypersil BDS C18 column 5um, 2.1 x 50mm

Micromass MassLynx™ Operating Software with OpenLynx™ Browser Option (V3.5 or better)

Waters Millennium^{32} ™ Chromatography Data System (V3.2 or better)

4.2 Instrumentation

4.2.1 Micromass Single Quadrupole LCMS systems ("MS1", "MS4", "MS6" or "MS7"), comprising:

Agilent HP1100 LC system comprising the following modules:

- G1315A Diode Array Detector or G1314A Single Wavelength UV Detector
- G1312A Binary Pump with Pulse Dampener and Mixer fitted
- G1316A Vacuum Degasser (optional)
- G1316A Column Oven (optional)

Polymer LabsPL1000 Evaporative Light Scattering Detector (ELSD)
with either

- CTC Analytics HTC PAL Autosampler

or

- Gilson 215 Single Probe Autosampler

with either

- Micromass Platform LC

or

- Micromass ZMD single quadrupole mass spectrometer

4.2.2 Micromass LCT systems ("MS5", "MS8" or "MS9"), comprising:

MS5

- Agilent HP1100 LC system comprising the following modules:

- G1314A Single Wavelength UV Detector
- G1312A Binary Pump with Pulse Dampener and Mixer fitted
- CTC Analytics HTC PAL Autosampler
- Micromass LCT with Z-spray Interface

MS8

- Waters 600 Binary Pump
- 8 x Waters 2487 Dual Wavelength Detector
- Gilson 215 Multiprobe 8-way Autosampler
- Micromass LCT with MUX™ 8-way interface

MS9

- Waters1525 Binary Pump
- 1 x 2488 Dual Wavelength 8-way detector
- CTC Analytics HTS PAL Autosampler with 4-fold injection valve
- Micromass LCT with MUX™ 5-way interface

5. LC Conditions

5.1.1 LC Conditions - for MS8.

Flow rate = 8.0 ml/min - split 8 ways to deliver 1ml/min through all 8 lines

Time (mins)	%B
0	0
1.80	95
2.10	95
2.30	0
2.90	0

5.1.2 LC Conditions - for MS9.

Flow rate = 4.0 ml/min - split 4 ways to deliver 1ml/min through all 4 lines

Time (mins)	%B
0	0
1.80	95
2.10	95
2.30	0
2.39	0

5.2 Mass Spectrometer Conditions

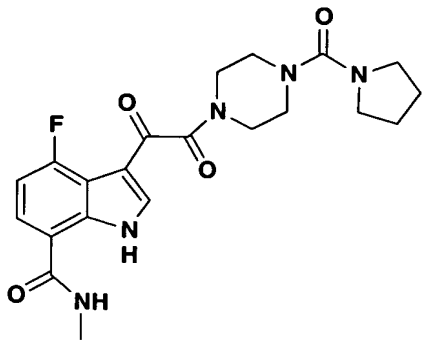
Data is typically collected over the range m/z 150 to 850 at a sampling rate of 2 scans per second (1 scan per 1.2 seconds per line on MS8).

6. Integration and Reporting

Data is integrated using OpenLynx and reported via the OpenLynx Browser software.

Example #	Exact Mass	HPLC Method	HPLC Ret. Time	Mass spec MH+, purity
Example 11	456.16	10 Min.	4.38 min.	457.31, 100%
Example 12	470.14	10 Min.	6.10 min.	471.36, 100%
Example 13	431.16	10 Min.	4.90 min	432.41, 100%
Example 14	528.16	10 Min.	4.36 min..	529.28, 46%

Preparation of Compound of Example 15



The compound of Example 15 was prepared from intermediate 2 following the procedure described for preparation of example 2, using 1-Pyrrolidinecarbonyl chloride as the acylating agent . ^{1}NMR (300 MHz, $CDCl_3$): 8.10 (d, 1H, J = 3.0 Hz); 7.42 -7.39 (m, 1H); 6.97 - 6.93 (m, 1H); 6.45 (bs, 1H); 3.80 (m, 2H); 3.55 (m, 2H); 3.40-3.25 (m, 8H); 3.04 (d, 3H, J = 5.0 Hz); 1.83 (m, 4H). MS (ESI^+): 430 $(M+H)^+$.

Biology

- "μM" means micromolar;
- "mL" means milliliter;
- "μl" means microliter;
- "mg" means milligram;

The materials and experimental procedures used to obtain the results reported in Tables 1-2 are described below.

Cells:

- Virus production-Human embryonic Kidney cell line, 293T, was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, CA) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO).

- Virus infection- Human epithelial cell line, HeLa, expressing the HIV-1 receptor CD4 was propagated in Dulbecco's Modified Eagle Medium (Invitrogen, Carlsbad, CA) containing 10% fetal Bovine serum (FBS, Sigma, St. Louis , MO) and supplemented with 0.2 mg/mL Geneticin (Invitrogen, Carlsbad, CA).

Virus-Single-round infectious reporter virus was produced by co-transfecting human embryonic Kidney 293 cells with an HIV-1 envelope DNA expression vector and a proviral cDNA containing an envelope deletion mutation and the luciferase reporter gene inserted in place of HIV-1 nef sequences (Chen et al, Ref. 41). Transfections were performed using lipofectAMINE PLUS reagent as described by the manufacturer (Invitrogen, Carlsbad, CA).

Experiment

1. HeLa CD4 cells were plated in 96 well plates at a cell density of 1 X 10^4 cells per well in 100 µl Dulbecco's Modified Eagle Medium containing 10 % fetal Bovine serum and incubated overnight.

2. Compound was added in a 2 µl dimethylsulfoxide solution, so that the final assay concentration would be ≤10 µM.

3. 100 µl of single-round infectious reporter virus in Dulbecco's Modified Eagle Medium was then added to the plated cells and compound at an approximate multiplicity of infection (MOI) of 0.01, resulting in a final volume of 200 µl per well.

4. Virally-infected cells were incubated at 37 degrees Celsius, in a CO_2 incubator, and harvested 72 h after infection.

5. Viral infection was monitored by measuring luciferase expression from viral DNA in the infected cells using a luciferase reporter gene assay kit, as

described by the manufacturer (Roche Molecular Biochemicals, Indianapolis, IN). Infected cell supernatants were removed and 50 µl of lysis buffer was added per well. After 15 minutes, 50 µl of freshly-reconstituted luciferase assay reagent was added per well. Luciferase activity was then quantified by measuring luminescence using a Wallac microbeta scintillation counter.

6. The percent inhibition for each compound was calculated by quantifying the level of luciferase expression in cells infected in the presence of each compound as a percentage of that observed for cells infected in the absence of compound and subtracting such a determined value from 100.

7. An EC_{50} provides a method for comparing the antiviral potency of the compounds of this invention. The effective concentration for fifty percent inhibition (EC_{50}) was calculated with the Microsoft Excel Xlfit curve fitting software. For each compound, curves were generated from percent inhibition calculated at 10 different concentrations by using a four paramenter logistic model (model 205). The EC_{50} data for the compounds is shown in Table 2. Table 1 is the key for the data in Table 2.

Results

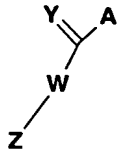
Table 1. Biological Data Key for EC_{50}s

Compounds* with EC_{50}s >5µM	**Compounds with EC_{50}s >1 µM but <5µM**	**Compounds with EC_{50} < 1 µM**
Group C	**Group B**	**Group A**

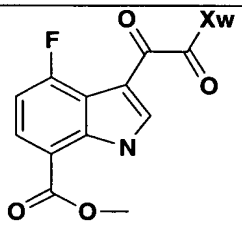
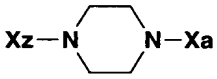
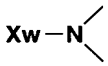
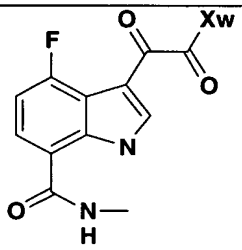
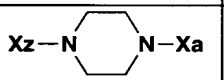
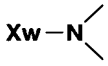
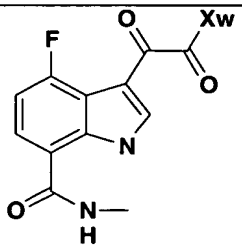
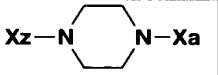
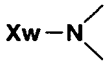
*Some of these compounds may have been tested at a concentration lower than their EC_{50} but showed some ability to cause inhibition and thus should be evaluated at a higher concentration to determine the exact EC_{50}.

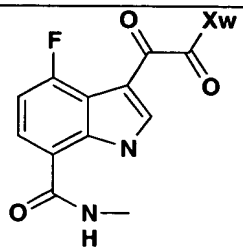
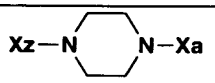
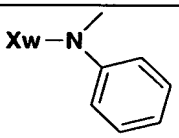
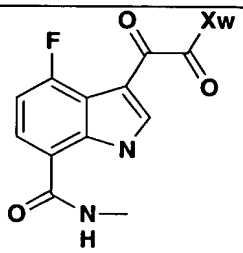
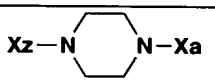
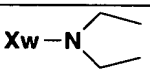
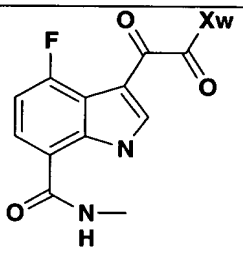
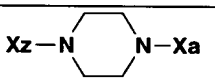
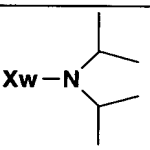
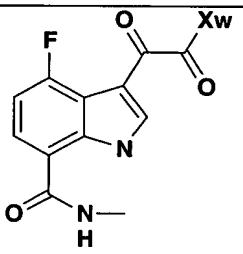
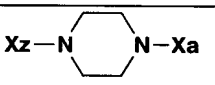
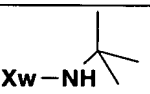
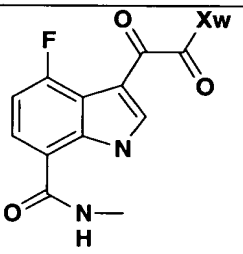
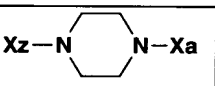
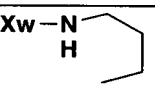
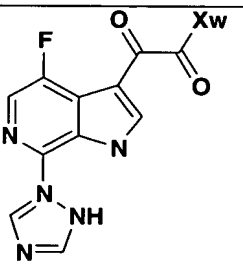
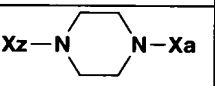
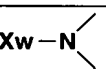
In Table 2, X_z, X_a and X_w indicate the point of attachment.

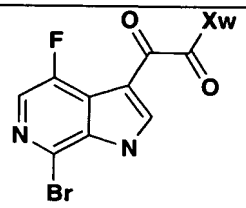
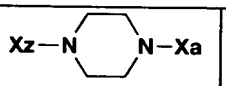
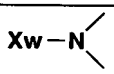
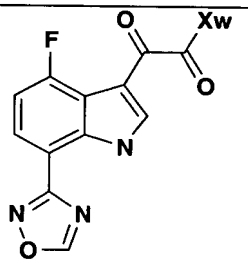
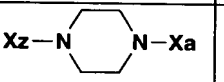
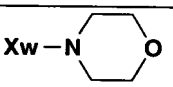
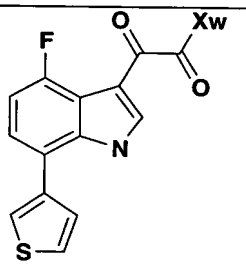
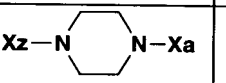
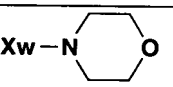
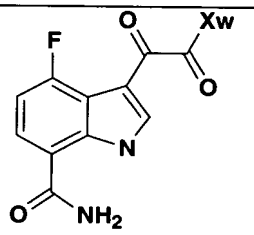
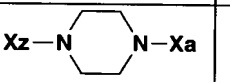
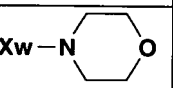
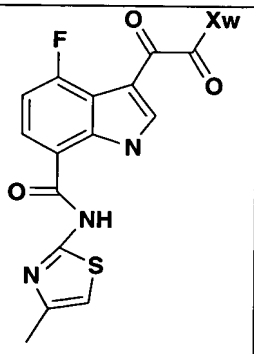
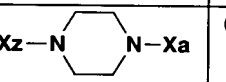
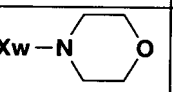
Table 2

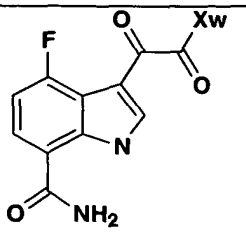
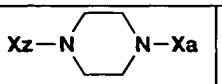
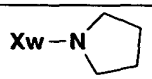


Examples

Table Entry (Example Number.)	Z	W	Y	A	EC_{50} Group from Table 1
1 (Example 1)			O		B
2 (Example 2)			O		A
3 (Example 3)			S		A

4 (Example 4)			O		B
5 (Example 5)			O		B
6 (Example 6)			O		C
7 (Example 7)			O		C
8 (Example 8)			S		C
9 (Example 9)			O		A

10 (Example 10, intermediate 7)			O		A
11 (Example 11)			O		B
12 (Example 12)			O		
13 (Example 13)			O		
14 (Example 14)			O		

15 (Example 15)			O		B

The compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and diluents.

Thus, in accordance with the present invention, there is further provided a method of treating and a pharmaceutical composition for treating viral infections such as HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically effective amount of a compound of the present invention.

The pharmaceutical composition may be in the form of orally administrable suspensions or tablets; nasal sprays, sterile injectable preparations, for example, as sterile injectable aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweetners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium

phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents, and lubricants known in the art.

The injectable solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 100 mg/kg body weight in divided doses. One preferred dosage range is 1 to 10 mg/kg body weight orally in divided doses. Another preferred dosage range is 1 to 20 mg/kg body weight in divided doses. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.